

# XIX.

## National Institute of Mental Health

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### INTRODUCTION

The National Institute of Mental Health (NIMH) is a scientific organization dedicated to the support and conduct of research focused on the understanding, prevention, and treatment of mental disorders and the promotion of mental health. NIMH is one of 25 Institutes and Centers of the National Institutes of Health (NIH), the principal biomedical and behavioral research agency of the U.S. Government and part of the U.S. Department of Health and Human Services (DHHS). Authorized in 1946, NIMH was one of the first NIH Institutes.

Mental illness is a serious burden for the global population; 5 of the 10 leading causes of disability are brain and behavioral disorders—unipolar major depression, alcohol use, bipolar disorder, schizophrenia, and obsessive-compulsive disorder. Depression is the leading cause of disability in the United States and in other established market economies. In the United States, depression affects 5% of the population over the course of their lives. Other global health-related issues that have a behavioral and mental health component include transmission of human immunodeficiency virus (HIV) and other sexually transmitted diseases (STDs), drug and tobacco use, intentional injuries, perinatal problems, and lifestyles contributing to chronic general medical illnesses.

Through research in basic neuroscience, behavioral science, and genetics, NIMH and the scientists it supports seek to gain an understanding of the fundamental mechanisms underlying thought, emotion, and behavior and an understanding of what goes wrong in the brain in mental illness. The Institute endeavors, at the same time, to hasten the translation of this basic knowledge into clinical research leading to interventions that will address appropriately and effectively the needs of diverse populations who seek and obtain treatment for mental illness, in a context of evolving health care systems.

### Research Areas

Key areas of NIMH-sponsored research include brain science, genetics, behavior, treatment, mental health of children and adolescents, brain imaging, and disparities in susceptibility to, prevalence of, and access to care for specific mental and behavioral disorders.

**Brain science.** Neuroscientists are gaining the ability to determine how brain cells and circuits function to enable cognition, emotion, and behavior. This progress further challenges researchers to apply this fundamental knowledge—along with information about how the brain changes as it develops and ages—to reveal precisely which parts of the brain are disturbed in mental illness.

**Genetics.** The completion and full draft sequence of the human genome provides enormous impetus to ongoing efforts to identify the genes responsible for vulnerability to mental and behavioral disorders. Combined with growing knowledge about the inheritance of these disorders in families and with information about the environmental triggers needed to activate vulnerability, the genetics revolution permits the anticipation of “cures” for mental illnesses.

**Behavior.** The explosion in new knowledge about the genetics, structure, and function of the brain challenges behavioral scientists to radically expand the traditional boundaries and methods of their discipline to determine how specific behaviors are directed and influenced by genes, how behavior can modify brain biology, how behavioral treatments for mental disorders can be strengthened, and how behavioral strategies for the prevention of diseases can be refined.

**Treatment.** With greater understanding about brain mechanisms involved in memory, decision making, and emotional responses to traumatic events, there is a growing need to revisit and redesign many of the current treatments. Translation of

basic science findings into innovative behavioral and pharmacological treatments that can either correct or compensate for brain dysfunctions will present immediate benefits to patients, family members, and clinicians. Large-scale trials of clinical effectiveness provide needed information on how well specific treatments work for real patients in actual practice settings.

**Mental health of children and adolescents.** Childhood and adolescence are critical developmental periods that have lifelong ramifications for mental health. Among immediate challenges to researchers are recognizing the precursor forms of adult mental illnesses and how and when to intervene with preventive measures in high-risk situations; designing the most effective mental health care services for children and adolescents; and recognizing the biological, behavioral, and environmental roots of violence and aggression, to facilitate timely and effective intervention.

**Brain imaging.** Advances in the temporal and spatial precision of brain-imaging technologies are being matched by reductions in cost and invasiveness of procedures. The net effect is to enhance the practicality of approaches that will image brain function in real time and over periods of development. The monumental challenge today is to link technological prowess to activation models capable of illuminating the complexities and subtleties of brain dysfunction at the onset and during the course of specific mental disorders.

**Disparities in mental health.** Globally, gender and social, cultural, or ethnic factors are known to increase the susceptibility of some groups of people to certain mental and behavioral disorders. Their access to and use of mental health care services, response to treatment, and resiliency may be influenced by the same factors. NIMH is dedicated to broadening the diversity of mental health researchers with the expertise and commit-

ment to identify and accommodate for these factors.

### **Research Programs**

The NIMH research enterprise has two major organizational and funding components. Through its extramural research program, NIMH supports more than 2,000 grants and contracts at universities and other institutions across the country and overseas. The extramural research grant system is premised on *independence*, embodied in “investigator-initiated” research; on *self-governance*, evident in peer review of science by scientists, as the primary basis for judging the merits of research proposals and award of funding; and on the powerful incentive of *competition* among scientists. The Institute’s three major extramural components are the Division of Basic and Clinical Neuroscience Research; the Division of Mental Disorders, Behavioral Research, and AIDS (acquired immunodeficiency syndrome); and the Division of Services and Intervention Research.

NIMH also administers the Intramural Research Program, which consists of approximately 500 scientists in 25 Laboratories and Branches on the NIH campus, Bethesda, Maryland. Intramural scientists include molecular biologists, geneticists, and behavioral scientists who conduct research on fundamental processes and clinical investigators who work with patients at the NIH Warren Grant Magnuson Clinical Center. The stable funding available through the Program makes possible long-term clinical studies that would be difficult for extramural researchers to accomplish. Also, because it involves basic science as well as clinical research, the Program is structured to facilitate interdisciplinary studies. In fiscal year 2000 (FY 00), the NIMH Intramural Research Program initiated a major strengthening of its research program on mood and anxiety disorders.

## **HIGHLIGHTS OF RECENT SCIENTIFIC ADVANCES RESULTING FROM INTERNATIONAL ACTIVITIES**

### **Russia**

In FY 98, under the Health Committee of the U.S.-Russia Joint Commission on Economic and Technological Cooperation, a program for detection and treatment of depression in primary health care settings was developed

in four Russian cities (Dubna, Moscow, Tomsk, and Yaroslavl) under the leadership, on the Russian side, of the Director of the Moscow Institute of Psychiatry. In FY 99, the Health Committee merged the program on depression with other primary care programs directed at treatment of chronic medical conditions, such as hypertension, asthma, and diabetes mellitus. The programs were merged in a new component entitled Access to Quality Health Care, under the purview of the Director of the Agency for Health Care Research and Quality, who served as the DHHS Secretary’s point of contact with the Russian Minister of Health.

Because the goal of merging several primary care programs was to achieve better management of chronic conditions in a primary care setting, a new site for treating depression was opened in FY 99, in Tula. This site was selected because it was an existing site for evidence-based treatment of arterial hypertension.

By the end of FY 00, primary care physicians and nurses had performed screening for symptoms of depression in more than 4,500 patients who visited the five primary care outpatient clinics (polyclinics). Subsequent diagnostic consultation by psychiatrists, based on criteria of the *International Classification of Diseases, 10th revision (ICD-10)* and assessment of the severity of depression, resulted in diagnosis of depression in about 30% of the patients who received screening. About 20% of the patients agreed to be treated with antidepressants and completed the treatment course conducted by psychiatrists in consultation with primary care physicians. Of the patients who received treatment, 90% had significant reduction of depression symptoms or complete remission. The level of responsibility carried by the primary care physicians and nurses in the process of diagnosis and treatment is expected to increase gradually.

Given the historical separation of specialty psychiatric services and primary care settings in Russia, the Russians have made substantial progress in demonstrating the feasibility of linking specialists with primary care providers. This approach has challenged long-held beliefs that only psychiatrists within the traditional referral process can provide effective psychosocial and psychopharmacological management of depressive illness.

To disseminate this model to other programs and sites in Russia, the Director of the Moscow Institute of Psychiatry and his colleagues conducted two training workshops for primary care physicians, which were sponsored by the American International Health Alliance. The Moscow Institute of Psychiatry developed the Methodological Recommendations on the Organizational Model of Care for Depressed Patients in Territorial Polyclinics, and these recommendations were approved by the Russian Ministry of Health. The limited funding for this demonstration has been raised almost entirely by the Russians from non-U.S. pharmaceutical firms and from the donation of time and facilities at each of the five sites for detection and treatment of depression in primary health care settings.

### **World Health Organization**

In FY 00, the World Health Organization (WHO) sponsored a consultation with leading mental health consultants to focus the WHO agenda for mental health. The NIMH Associate Director for Epidemiology and Health Policy Research and the Director of the Division of Services and Intervention Research contributed to that consultation in January 2000. More recent follow-up consultations with NIMH staff and other international consultants have led to the development plans for a focus on primary health care programs for treatment of depression and suicide prevention.

### **Revision of International Classification of Impairments, Disabilities, and Handicaps**

Throughout FY 00, the International Task Force on Mental Health and Addictive, Behavioral, Cognitive, and Developmental Aspects of the *International Classification of Impairments, Disabilities, and Handicaps (ICIDH)* actively contributed to the revision process for the WHO *ICIDH*. The charge of the International Mental Health Task Force continued to be focused (1) on the mental health aspects of the *ICIDH* revision, the unique contributions of mental functions and structure for which the task force has responsibility, and (2) on the impact of mental disorders on performance of activities and participation in society.

Also during FY 00, the field trials of the beta-2 of *ICIDH-2* were completed, analyses

of the five mandatory components were conducted by WHO, and the revised version of *ICIDH-2* was submitted for approval. The International Mental Health Task Force played a leading role in the revision process, especially in developing operational definitions of mental functions and of the activities that most characteristically reflect the limitations experienced by people with mental disorders, such as those related to work and social relations.

With the foundation laid by the International Mental Health Task Force, at least 22 countries participated in the revision process and the field trials. During FY 00, NIMH contributed funding as seed money for the conduct of the field trials for both the International Mental Health Task Force and La RHHD (La Red de Habla Hispana en Discapacidades).

### **WHO-NIH Joint Project on Assessment of Disabilities**

In the WHO-NIH Joint Project on Assessment of Disabilities, the National Institute on Alcohol Abuse and Alcoholism, the National Institute on Drug Abuse (NIDA), and NIMH are working with WHO to develop research instruments with versions to assess disabilities in epidemiologic and clinical investigations. In FY 00, the 5th of 5 years planned for this research effort, the project neared successful completion. The development of the *WHO Disability Assessment Schedule II (WHO DAS II)* has primarily focused on the structured epidemiologic version. The strategy is that the clinical version will essentially telescope from the foundation laid by the shorter epidemiologic version and will have a semistructured interview format. Preliminary work on the clinical version and on computer-assisted and proxy versions of the survey instrument was undertaken in FY 00.

The survey version of *WHO DAS II* queries six domains of disability—understanding and communicating, getting around, self-care, getting along with people, life activities (work and household), and participation in society. This questionnaire is designed to obtain data on both the amount and frequency of difficulty experienced in each area. Qualitative and quantitative field trials and testing of the instrument's psychometric properties were conducted in 21 centers in 19 countries, to ensure international ap-

plicability, relevance, and reliability. During FY 00, pilot studies were conducted to test *WHO DAS II* in research on health services.

A supplement to the Cooperative Agreement that supports this joint project is dedicated to development of a method for using an empirical base as a disability weight in assessment of the global burden of disease, a measure of worldwide disease created by WHO, the World Bank, and Harvard University, Cambridge, Massachusetts. This disability weight would be applied to determine the years lived with a disability, which is a component of disability-adjusted life years. In the past, disability weights for years lived with a disability have been determined through preference valuation techniques from the field of economics, but these techniques may not be sufficiently sensitive to changes in disability status in response to health care treatment and interventions. Data on disability were collected in several countries by using *WHO DAS II*. These data are being used (a) to develop a method that can apply an empirically based global measure of disability that is sensitive to change and (b) to compare relative disability weights across health conditions and assessment techniques.

### **Center for Mental Health Research on AIDS**

"We put absolutely too much emphasis on treatment and too little on prevention....A trillion dollars a year we spend in our health system, and 1% of that is for population based prevention. We depend upon biotechnology. We believe that we can solve anything with it. And it's just not true and it becomes less true every day that we live."

Dr. David Satcher,  
U.S. Surgeon General, 1998

Behavioral prevention is today's AIDS vaccine, and it is imperative that prevention programs be scaled up internationally to prevent a more disastrous AIDS epidemic. The Joint United Nations Program on HIV/AIDS (UNAIDS) has estimated that only 10% of the funds for research on and treatment of HIV/AIDS are expended in countries that are experiencing 90% of the epidemic. NIMH has made a major commitment to the development of an international HIV/STD behavioral prevention program. The goals for the NIMH AIDS program are

(1) to extend the generalizability of efficacious primary and secondary preventive interventions to international settings; (2) to identify assumptions and cultural issues in prevention programs; and (3) to understand the situational determinants and dynamics of AIDS prevention in multicultural settings. Priority research areas include programs focused on the following:

1. behavior change programs for youth;
2. voluntary counseling and testing for couples;
3. the role of stigma, shame, and disclosure in HIV/STD prevention;
4. the role of gender, power, violence, and discrimination in HIV/STD transmission;
5. structural interventions (social norms about risk behaviors, new economic opportunities, and syndromic treatment of STDs [on the basis of reported symptoms]), and primary prevention programs designed for HIV-infected persons to ensure that they do not transmit HIV to uninfected persons, to slow the progression of the disease, and to enhance their quality of life; and
6. the role of family in preventing and adapting to HIV/AIDS.

### **AIDS Research Centers**

NIMH supports AIDS Research Centers that actively promote international collaborations. The HIV Center for Clinical and Behavioral Studies, at Columbia University, New York City, New York, has a history of collaborative relationships in Brazil, Puerto Rico, and South Africa. Both NIMH and the John E. Fogarty International Center for Advanced Study in the Health Sciences (FIC) are contributing to building infrastructure to conduct extensive epidemiologic studies on HIV/STD. Specific programs focus on integrating pregnancy prevention and disease prevention in Brazil and prevention of HIV risk behaviors in the mentally ill in South Africa.

The Center for AIDS Prevention Studies, at the University of California, San Francisco, builds partnerships between scientists at the Center and scientists from Africa, Asia, Eastern Europe, and Latin America. Together the scientists are examining risk behavior patterns, to develop AIDS prevention programs that are appropriate for the country. Examples of research are an epidemiology study in Brazil and a project on HIV-related risk behavior patterns in men in Zimbabwe. This

Center is participating in the NIMH Collaborative HIV/STD Prevention Trial.

The Center for AIDS Intervention Research, Milwaukee, Wisconsin, has been collaborating on training and the initiation of studies in St. Petersburg, Russia, and is exploring prevention projects in other Eastern European countries and Puerto Rico. The alarming prevalence of STDs among youth has prompted the initiation of these programs. The Center is one of the institutions in the NIMH Collaborative HIV/STD Prevention Trial.

The Center for Early Detection, Prevention, and Treatment of HIV, at the University of California, Los Angeles (UCLA), has started an international program. The researchers are studying the risk patterns for vulnerable populations, such as homeless youth and disenfranchised women, in Australia, India, and Russia. This Center is also one of the sites in the NIMH Collaborative HIV/STD Prevention Trial.

### **International Research Studies NIMH Collaborative HIV/STD Prevention Trial**

The NIMH Collaborative HIV/STD Prevention Trial is a two-arm, randomized, community-level trial conducted in six countries—China, India, Peru, Russia, Uganda, and Zimbabwe. This trial is sponsored by NIMH and FIC, at the NIH.

Effective individual prevention approaches are not rapid enough to avert the AIDS epidemic, and they are too resource intensive. Community-level interventions to produce behavior change have the potential to reach a large number of people and to be cost-effective and feasible, even in areas with limited resources. NIMH is therefore supporting the first international test of a community-level prevention program based on the theory of diffusion of innovations through popular opinion leaders in the community. The program has been tested in multicultural populations in multiple sites in the United States.

This intervention engages community public opinion leaders (C-POLs) to serve as agents for behavior change to friends and neighbors in their community. Because this strategy relies on the strong oral traditions in the countries involved, it is expected to be effective in strengthening norms about safer sexual behavior and encouraging reduction

of HIV/STD risk among people in high-risk communities.

This trial has already made some methodological contributions. For example, the ethnographic component is an integral part of understanding the context and meaning of risk behaviors of persons in the social networks; designing the intervention; developing the assessment devices; and ultimately, evaluating the impact of the intervention. The investigators have also been conducting a reliability and validity study by using Audio Computer Assisted Self Interview (A-CASI) and Computer Assisted Patient Interview (CAPI) to identify the role of modality versus wording of questions in assessment of risk behaviors in different countries. The prebaseline questionnaire has been translated into 12 languages, and a detailed protocol for collecting and analyzing biospecimens in six countries has been established and is being field tested.

### *HIV/AIDS Prevention Trials Network*

NIMH is one of the four Institutes at the NIH to cosponsor the HIV/AIDS Prevention Trials Network (HPTN). The HPTN will support both domestic and international studies of prevention programs, with HIV incidence as an outcome. Twenty-seven sites are collaborating in this network. Protocols are in development as proposed by the six Workgroups—Behavioral, Sexually Transmitted Diseases, Vaccines, Anti-Retroviral Therapy, Microbicides, and Substance Use. An NIMH staff member serves on the Behavioral Workgroup and on the Prevention Leadership Group.

### **Multicountry Internet Study**

NIMH is supporting an innovative, Internet-based, phase IV study of HIV prevention through technology transfer. The investigators will develop and evaluate the effectiveness of an interactive Internet program for transferring efficacious HIV prevention models from research settings to non-governmental organizations (NGOs) in developing countries with high HIV incidence. Eighty NGOs in Africa, Central and Eastern Europe, and Latin America will be enrolled in the study and randomly assigned to one of two conditions. Forty NGOs will receive the experimental condition—the Public Opinion Leader (POL) intervention manual and materials and 6 months of technical

assistance, delivered over the Internet, on how to implement the POL intervention. The 40 NGOs in the control condition will receive only the POL intervention manual and materials. Six and 12 months later, the staff at all 80 NGOs will be assessed to evaluate (1) adoption of the POL intervention as part of the NGO prevention program, (2) any tailoring or adaptations that were required, (3) staff attitudes and satisfaction with the intervention, and (4) implementation costs. If effective, the Internet intervention will be delivered in the control NGOs. This study will make multiple contributions to prevention science: (1) increase knowledge about transferring effective research-based HIV prevention approaches to community-based service providers; (2) develop and test a prototype model for using advanced, intervention-based approaches for technology transfer; and (3) allow HIV prevention research advances to benefit epicenters of HIV and STDs.

This is the first test of the Internet as a mechanism to stimulate NGOs to adopt new, cost-effective prevention programs as part of their repertoire. The research partially replicates a study in the United States that had the same objectives but delivered the training in face-to-face workshops and conducted the technical assistance on the telephone. That method would not be feasible internationally.

### **Australia**

There is substantial risk for HIV associated with long-term homelessness among youths. To assess the impact of policies and programs on the developmental trajectories of risk for first-time homeless youths, a comparative study is being conducted in Australia and the United States. Australia differs from the United States in policies of harm reduction, needle exchange, national programs for positive sexual health, and the organization and distribution of community resources for homeless youths. Longitudinal data will be collected at recruitment to the study and at 3, 6, 12, 18, 24, 30, and 36 months, across four domains: (1) individual risk for HIV, (2) street experiences, (3) context of peers' risk acts and community factors, and (4) background characteristics of the youths and their families. Study results are expected to enhance understanding of the social and structural context of youths'

developmental trajectories, so that an intervention can be designed for first-time run-aways, to interrupt behaviors that increase risk of HIV.

### **Caribbean**

In the Caribbean, seroprevalence of HIV as a percentage of the population is second only to that in sub-Saharan Africa. The Trinidad and Tobago HIV Prevention Project proposes a training and mentoring partnership between the Chicago (Illinois) HIV Prevention and Adolescent Mental Health Project (CHAMP) and the Family Planning Association of Trinidad and Tobago. CHAMP is a developmentally based program for primary prevention of HIV that has been developed and tested with ethnic minority youths and their families in Chicago. All stages of the original program involve close collaboration between CHAMP staff and community residents to ensure that the program is culturally relevant. This approach will also be used in the Caribbean study.

The Center for Mental Health Research on AIDS, at the University of Puerto Rico, San Juan, has developed a comprehensive research program supported by NIMH. Several projects are addressing AIDS prevention. One project is testing a primary prevention program (four 2-hour sessions) with urban youths who are at or near the age of sexual initiation and their parents and teachers. The other project will refine, adapt, and transfer an empowerment-intervention model targeting HIV-positive homosexual men that is expected to increase safer sex practices and health behaviors. NIMH staff participate in an annual site visit to provide technical assistance on HIV/STD prevention.

### **India**

NIMH has made a major commitment to support behavioral prevention research in India, and several projects are being conducted by NIMH investigators. Together, Johns Hopkins University, Baltimore, Maryland, and the YRG Centre for AIDS for Research and Education (CARE), Chennai, comprise one of the six teams implementing the NIMH Collaborative HIV/STD Prevention Trial, in Chennai. The World AIDS Foundation also supports some collaborations among NIMH investigators.

In addition, investigators at Johns Hopkins University and YRG CARE, Chennai,

are conducting a study to assess the relationship of alcohol consumption and HIV risk in urban India. They are documenting the rates of alcohol use and HIV risk behaviors. The location, size, and clientele of "wine shops" and local "arrack" vendors will be mapped to determine their proximity to commercial sex venues and slum housing. In addition, an ecological analysis of the association between alcohol availability and pricing (both legal and illegal) and self-reported risk for HIV will be documented. Ethnographic research will identify gender differences in reasons for drinking alcohol, social network affiliations of men and women who frequent wine shops, and sexual promiscuity. A quantitative survey on drinking patterns and practices related to HIV risk behavior among urban slum dwellers will be developed and administered. Finally, the researchers will develop an intervention designed to influence HIV sexual risk behaviors among male slum dwellers in this community.

A study is being conducted by the University of Connecticut in collaboration with the Benzinger Foundation, Chennai, to increase safer sexual behavior in a high-risk population of truck drivers in India. Based on preliminary work, this research team has described the dynamics of HIV risk behaviors, especially (a) high rates of unprotected sexual intercourse with commercial sex workers and nonmarital partners and (b) failure of the men to use condoms with their wives. Based on these data, an intervention is being implemented with truck drivers that addresses the profound deficits in information, motivation, and behavioral skills that result in extremely high-risk behaviors.

Investigators from Yale University, New Haven, Connecticut, are conducting a study in India to increase understanding of the social stigma of HIV and its role in fueling the AIDS epidemic. For this study, 108 persons are being recruited from six locations throughout India, to explore the dimensions of stigma that are relevant to HIV in different aspects of Indian society. Findings from this initial qualitative research will be used to design a survey instrument to elicit information about the stigma of HIV from a broader sample. The survey will be administered to 3,000 respondents, and the findings will provide the basis for a larger, more representative investigation of HIV-related

stigma in Indian society. These data will be used to develop a culturally relevant intervention to address stigma in primary AIDS prevention.

Researchers at UCLA and the Indian Council on Medical Research, New Delhi, are conducting a study to identify HIV/STD risk factors for Indian women and are developing an intervention that will integrate disease prevention and reproductive health, for use in clinics. This team is also performing a study of STDs in women. The first randomized clinical trial of an HIV/STD intervention for women in Calcutta is being conducted by a researcher from UCLA and an Indian physician who developed this comprehensive empowerment program for AIDS prevention. This study will be expanded to two additional communities to generalize the results.

### **Zimbabwe**

Children are bearing a large part of the burden of AIDS in sub-Saharan Africa, and the number of households headed by a child is increasing, as parents become sick and then die of AIDS. A study of children who are caring for HIV-infected parents or who are orphans due to their parents' death from AIDS is being conducted in Mutare by investigators from the AIDS Orphan's Project, a private African foundation, and the Einstein College of Medicine, Bronx, New York. The aims of this study are (1) to document the education, mental health, and duties of children who have assumed adult roles prematurely and (2) to assess the long-term consequences to these children, their siblings, and the community.

Many urban and rural adolescent girls living in Zimbabwe engage in or are at risk for engaging in sexual activity for economic necessities (compensated sex), to cover living expenses. One study focuses on girls aged 13–19 years who are not in school, a difficult population to access. The specific aims of this research are (1) to gather information on the socioeconomic and behavioral determinants of participating in compensated sexual relationships and (2) to characterize these girls in terms of risk behavior, reproductive health status, and school and employment history. In addition, some methodological issues are being addressed, such as identification of recruitment and tracking strategies necessary to enroll and retain these girls in

a study and methods to obtain informed consent from minors and their parents. On the basis of these data, an intervention, probably with an economic component, will be developed and tested.

Traditional healers provide the majority of care and treatment for HIV infection in rural Zimbabwe. An investigator from the University of Pennsylvania, Philadelphia, is engaged in describing the healing process for the healer and the patient, in the Shona therapeutic process. The research design involves group comparisons among the spirit mediums, diviners, and biomedical care group.

### **NIMH AIDS Strategic Intervention Simulation Tool**

At the beginning of this third decade of the AIDS epidemic, prevention programs will continue to have an essential role. Even if generic drugs and licensed in-country products were widely available, public and private philanthropy would not be sufficient to provide effective treatment to the HIV-positive population in a country of even modest size. For example, the cost for treating the HIV-positive population in Zimbabwe has been estimated at \$18 billion in 2000. It is therefore imperative that prevention programs be scaled up as rapidly as possible. Prevention programs with multiple components are needed, and components should include voluntary counseling and testing; skills-building programs for behavior change; and multiple-level policies for individuals, couples, families, and communities.

NIMH has developed a behavioral prevention program that mathematically models the AIDS epidemic under various conditions of uncertainty. The NIMH AIDS Strategic Intervention Simulation Tool (NIMH/ASIST) can be used to provide estimates of the impact of introducing behavioral prevention programs at different times, focused on different high-risk populations and targeting different levels of behavior change. Data from this modeling program can be used by ministers of health, directors of NGOs, or directors of public health clinics, to distribute resources, set priorities for prevention programming, and dramatize the cost of not initiating behavioral prevention programs. This program was introduced at an invited symposium at the XIIIth International AIDS Conference, in Durban, South Africa, and

was demonstrated continuously at the NIMH AIDS booth.

### **International Meetings 3<sup>rd</sup> Indo-U.S. Workshop on Behavioral Prevention of HIV/STDs**

An NIMH delegation composed of eight prevention scientists, the Director, and three staff members participated in the 3<sup>rd</sup> Indo-U.S. Workshop on Behavioral Prevention of HIV/STDs, which was cosponsored by the Indian Council on Medical Research; the National AIDS Control Organization, New Delhi; FIC; and NIMH. Participants at the workshop drafted a joint Indo-U.S. agenda for research on behavioral prevention of HIV/STDs, which will be implemented under a joint agreement signed by representatives of India and the United States in July 2000. As a result of this collaboration, Indo-U.S. research teams are conducting eight studies of behavioral prevention. A fourth workshop is being planned for February 2002, in India.

### **8<sup>th</sup> Annual Russian Conference on AIDS, Cancer, and Related Diseases**

Members of the steering committee of the NIMH Collaborative HIV/STD Prevention Trial were invited to present a symposium on AIDS Prevention Programs That Work, at the 8<sup>th</sup> Annual Russian Conference on AIDS, Cancer, and Related Diseases, in St. Petersburg, on May 23–26, 2000. This trial is being conducted in six countries—China, India, Peru, Russia, Uganda, and Zimbabwe. The steering committee made a site visit to the student dormitories where the study is being conducted in St. Petersburg and held a 2-day scientific advisory meeting.

### **XIII<sup>th</sup> International AIDS Conference**

NIMH had a booth at the XIII<sup>th</sup> International AIDS Conference, in Durban, South Africa, on July 9–14, 2000. The theme of the booth—Behavioral Prevention Is Today's AIDS Vaccine!—was displayed on buttons and posters that were handed out as part of the educational campaign. In addition, NIMH/ASIST was introduced at an invited symposium and demonstrated at the booth. (For a more detailed description of NIMH/ASIST, see "International Research Studies" in the section on "Highlights of Recent Scientific Advances Resulting From International Activities.") The NIMH Director gave

an invited plenary talk on behavioral prevention, and four NIMH staff also attended this conference. During the conference, the NIMH AIDS Director participated in a joint meeting of the Gore-Mbeki Binational Commission on Health Working Group, to review the joint program initiatives.

### **Role of Families in Preventing and Adapting to HIV/AIDS**

NIMH sponsors an annual conference on the Role of Families in Preventing and Adapting to HIV/AIDS. International representatives from Mexico, Nigeria, and Peru were invited to participate at the conference, in Chicago, Illinois, on July 26–28, 2000. The theme was HIV/STD prevention in Hispanic families.

### **Future International Activities**

Investigators in the NIMH Collaborative HIV/STD Prevention Trial have been invited to present a symposium on this international trial at Cayetano Heredia University, in Lima, Peru. NIMH staff will meet with the Minister of Health to learn more about the AIDS epidemic in Peru and plans for HIV/STD prevention. The steering committee for this trial is also planning a site visit to the barrios where the trial will be conducted in Lima.

NIMH is planning a fourth Collaborative Indo-U.S. Workshop on Behavioral Prevention Programs, to be held in India, in February 2002. At this workshop, the strategic prevention plan developed in January 2000 will be reviewed. In addition, the Indian and U.S. investigators who are conducting studies will present their findings.

A workshop cosponsored by NIMH and the South African Medical Research Council will be held in Durban, in October 2000. A U.S. delegation of seven AIDS prevention scientists, four experts on violence, and four NIMH staff is planning to participate. The major objectives will be to review the current studies on HIV prevention and on violence, develop research priorities, and form collaborative research teams. The Director of the NIMH AIDS program will also be part of a DHHS delegation headed by the U.S. Surgeon General, to review the status of the Gore-Mbeki agreement in November 2000. NIMH staff are preparing a joint program for research on behavioral prevention, for review at this meeting.

NIMH is planning to issue a Request for Proposals entitled International Initiatives for HIV/STD Prevention. These initiatives are intended to support new research projects in international settings, beginning in September 2001.

## SUMMARY OF INTERNATIONAL PROGRAMS AND ACTIVITIES

### Activities With International and Multinational Organizations

#### International Cooperative Biodiversity Group Program

The International Cooperative Biodiversity Group (ICBG) Program is an innovative, interagency conservation and development program administered by FIC. The goal of the Program is to promote biodiversity conservation and sustained economic activity through the discovery and development of therapeutic agents derived from natural products (e.g., plants, fungi, insects, and microbes). The ICBGs consist of diverse public and private institutions, including universities, environmental organizations, and pharmaceutical companies. The ICBG Program is jointly funded by a consortium of Federal agencies, including the Biological Sciences Directorate of the National Science Foundation (NSF), the Foreign Agriculture Service of the U.S. Department of Agriculture, and five Institutes of the NIH: the National Cancer Institute (NCI), the National Institute of Allergy and Infectious Diseases, NIDA, the National Heart, Lung, and Blood Institute, and NIMH. The Neuropharmacology Program of NIMH contributes support to three of the ICBG projects: Biodiversity Utilization in Madagascar and Suriname, Drug Discovery and Biodiversity Among the Maya of Mexico, and Biodiversity of Vietnam and Laos.

The ICBG Program supports six projects in 10 countries in Africa, Asia, and Latin America: Argentina, Cameroon, Chile, Laos, Madagascar, Mexico, Nigeria, Panama, Suriname, and Vietnam. Projects include the selection and acquisition of natural products derived from biological diversity, as potential therapeutic agents for diseases, such as Alzheimer's disease, psychiatric disorders, drug addiction, cancer, AIDS, parasitic diseases, and heart disease, all of which are of concern to both developed and developing countries.

Numerous publications in chemistry, bio-

diversity policy, conservation, and ethnobiology have emerged from the funded investigators. Broad public attention to the Program and its timing relative to international developments associated with the United Nations Convention on Biological Diversity have allowed the ICBG Program to offer useful working models for national and international policy discussions related to biodiversity conservation incentive measures, technology transfer, intellectual property, and benefit sharing. Further information about the ICBG programs is available at <http://www.nih.gov/fic/programs/icbg.html>.

#### Organization for Economic Cooperation and Development

Since 1996, the Associate Director, Office on Neuroinformatics, NIMH, has chaired the Neuroinformatics Subgroup, Biological Working Group, Megascience Forum, of the Organization for Economic Cooperation and Development (OECD). In the United States, multiple agencies and multiple Institutes of the NIH support the Human Brain Project/Neuroinformatics Program. The supporting agencies are the NIH, NSF, the U.S. Department of Energy, and the National Aeronautics and Space Administration. The supporting Institutes of the NIH are FIC; the National Institute on Aging; the National Institute on Alcohol Abuse and Alcoholism; NCI; the National Institute of Child Health and Human Development; the National Institute on Deafness and Other Communication Disorders; the National Institute of Dental and Craniofacial Research; NIDA; the National Heart, Lung, and Blood Institute; NIMH; the National Institute of Neurological Disorders and Stroke (NINDS); and the National Library of Medicine.

The goals of this program are to create a set of distributed databases and tools to advance the field of neuroscience research. The driving force for this initiative in the United States is the ever-increasing amount of empirical research data generated at greater levels of granularity and sophistication, from the 30,000 neuroscientists in the United States. There is a great need to create modern databases at all levels of neuroscientific analysis and in a manner that will allow them to interoperate with other databases, such as the genome and proteomics databases. Such an effort will conserve this great wealth of data and allow for integration of

simulation of brain function across levels of analysis and modeling of brain structure, function, and development, to facilitate proper theoretical-experimental interplay. Because there are approximately 55,000 neuroscientists globally, all neuroscientists in all countries must participate to achieve the creation of an adequate knowledge-management system. This goal provides the impetus for the Neuroinformatics Subgroup of the OECD Megascience Forum.

The Neuroinformatics Subgroup of the OECD Megascience Forum issued its defining report as part of the full Biological Informatics Committee's report to the delegates, in January 1999 (see [http://www.oecd.org/dsti/sti/s\\_t/ms/index.htm](http://www.oecd.org/dsti/sti/s_t/ms/index.htm)). This report is summarized in the *National Institutes of Health Annual Report of International Activities, Fiscal Year 1999*. In January 2000, the United States and Italy recommended to the OECD Global Science Forum, the creation of a Global Science Forum-Neuroinformatics Working Group for 3 years. The three main goals of this Working Group are resource activities, database guidelines, and sustainability of the global informatics network.

**Resource activities.** Resource activities consist of collating and making available to the general community an inclusive list of neuroinformatics resources. This list will include neuroscience databases, neuroinformatics tools, and computational methods for modeling and simulating brain function. It will be generated by the members of the new Global Science Forum-Neuroinformatics Working Group and individual scientists and will also rely on input from national funding agencies.

**Database guidelines.** The Working Group will perform the following functions: (1) develop database guidelines for content, organization, and quality control and standards to ensure interoperability and longevity of the neuroscience databases; (2) develop a capability to facilitate the distribution of neuroinformatics tools and computational methods for modeling brain functions and to assist in maintenance of such tools and methods; and (3) start a dialogue about changes in the way researchers are evaluated and rewarded in an evolving field of shared databases and interdisciplinary collaboration.

**Sustainability of global informatics network.** To ensure sustainability of the global

informatics network, the Working Group is creating the Neuroinformatics Portal, an Internet-based knowledge repository for neuroinformatics applications and neuroscience data, providing electronic services (e-services) for scientists, governments, and citizens. The Working Group will develop an operational and business plan for its start-up, with government backing and maintenance through commercial support. The Working Group will collaborate with individual governments to establish National Neuroinformatics Nodes and to help in development of a list of responsibilities for these nodes, to sustain the global Neuroinformatics network.

After approval of this new Global Science Forum-Neuroinformatics Working Group for 2 years, the first meeting was held in Genoa, Italy, in May 2000, and the second meeting was held in Washington, D.C., in September 2000. The work plan for these meetings was to develop a united operational plan and to start implementing it in each country. The members of the Working Group include; Australia, Belgium, the Czech Republic, Denmark, the European Commission, Finland, Germany, India, Italy, Japan, Korea, the Netherlands, Norway, Poland, Portugal, Spain, Sweden, Switzerland, Turkey, the United Kingdom, and the United States.

### **U.S.-European Commission**

The U.S.-European Commission (U.S.-EC) Task Force on Biotechnology Research was established in 1990 and is cochaired by the Assistant Director, Biological Sciences, NSF, and the Director, Life Sciences Coordination, Directorate of General Research, European Commission. A joint U.S.-EC Neuroinformatics Steering Committee was established in 1995, under the auspices of this task force, to monitor and promote interactions and communications about collaboration on neuroinformatics research between the United States and the European Commission, across disciplines and national borders. The activities of this steering committee complement the activities of the Human Brain Project/Neuroinformatics Program and the Neuroinformatics Subgroup of the OECD Global Science Forum.

The year 2000 was the 10<sup>th</sup> anniversary of the U.S.-EC Task Force on Biotechnology Research. During the year, the Neuroinformatics steering committee of this task force

organized a symposium entitled Neuroinformatics: an Enabling Capability for Understanding and Integrating Brain Function, which was held at Collegium Internationale Neuro-Psychopharmacologicum, in Brussels, Belgium, in July 2000. This anniversary was noted at the annual meeting of the U.S.-EC Task Force on Biotechnology Research, in Brussels, in October 1999, and a 10<sup>th</sup> anniversary publication was released, with summaries of the accomplishments and activities of this task force. At that meeting, the plans from the Neuroinformatics steering committee to hold a joint workshop on Databases in Neuroscience, in Oslo, Norway, on July 12, 2001, were reviewed and affirmed. It was also suggested that a joint workshop be organized in 2001, to develop appropriate training curricula for the entire field of Biological Informatics, with a focus on genomics, neuroscience, and biodiversity.

### **Extramural Programs Office on Neuroinformatics**

#### *Research Grants*

The NIMH Office on Neuroinformatics, together with the National Institute of Child Health and Human Development, NIH, funded a joint research venture between two laboratories, at the University of Newcastle upon Tyne, England, and the Medical Research Council (MRC) Human Genetics Unit, Edinburgh, Scotland. These two research groups combine their collaborative expertise in human and mouse developmental genetics and the construction of three-dimensional digital atlases. The aim of this neuroinformatics research is to produce an interactive atlas and database of gene expression patterns in the human fetus, interfaced with similar tools for the murine model. The investigators are seeking to acquire high-resolution gene expression data for fetal human brain that will permit comparison with equivalent data being generated for animal models, notably the mouse. This will provide molecular anatomic landmarks of human fetal brain development to supplement existing standard anatomic landmarks. In addition, it will permit comparison of species' differences across animal models, most notably with the mouse. The investigators also plan to establish an interactive graphic database of high-resolution gene expression patterns in

human fetal brain, mapped onto an anatomic framework. Results from this research project can be used to enhance knowledge about human fetal brain development and to acquire new information and create novel tools for understanding developmental disorders of the human nervous system.

The NIMH Office on Neuroinformatics, together with NCI, NIDA, and NINDS, funded an ongoing collaborative program project at UCLA. This project is administered under the International Consortium for Brain Mapping, which comprises leading research institutions in Australia, Canada, England, Finland, France, Germany, Japan, the Netherlands, and the United States. The mission of this consortium is to create a global database representing a probabilistic reference system for the human brain. The focus of this multitiered study involves genetic, molecular, and cellular systems and the whole brain. The novel neuroinformatics tools being developed under this project include those for querying, retrieval, and databases; data presentation and analysis; data integration and synthesis modeling; and electronic collaboration. Results from this joint effort will allow access to, evaluation of, and internationally shared interpretation and communication about data acquired across 7,000 subjects, aged 18–90 years. The results will reflect ethnic and racial diversity and will provide abundant demographic, behavioral, clinical, imaging, and genetic data.

In addition, the NIMH Office on Neuroinformatics funded a program project center grant at the University of Minnesota/Veterans Affairs Medical Center, Minneapolis, to conduct modeling and visualization of spatial and temporal patterns in functional neuroimaging. The researchers used functional activation obtained from positron emission tomography (PET) and functional magnetic resonance imaging (fMRI), during a broad series of neurocognitive studies. The International Neuroimaging Consortium (INC) centers involved in this study are located in the United States, Canada, Denmark, and Japan. The project focuses on resolving differential temporal processes in cortical areas, with use of time-resolved, event-related fMRI, leading to landmark findings on spatiotemporal characteristics in the cat primary visual cortex.

Considerable progress has been made on

developing, assessing, and optimizing models for data analysis in experiments on functional neuroimaging. With use of various measures derived from PET and fMRI scanning, important advances have been made on development of statistical analysis techniques applicable to PET and fMRI data sets; on quantitative evaluation of bias-field-correction algorithms; and on establishment of relationships between behavioral and neuroimaging data. Additional key accomplishments include developing, distributing, and evaluating three-dimensional interactive visualization tools for use in cerebellar parcellation and flat mapping for functional neuroimaging. Finally, four major aims of INC involve (1) development of *repositories* as sets of libraries of computer software modules and toolboxes; (2) *communications* related to developing a basic support for collaborative work as a virtual "center without walls"; (3) *integration* by distribution of data sets from public programs; and (4) *dissemination* by distribution of software packages to other neuroscience resources on the Internet via the newly developed, publicly accessible INC knowledge base of software libraries.

On completion, it is anticipated that this work will be published and made available for distribution on the INC web site. Results from this project will provide neuroscientists and clinicians with powerful tools to explore data sets from fMRI, MRI, PET, and single photon emission computed tomography (SPECT).

Together, the NIMH Office on Neuroinformatics and NSF funded an international collaborative research grant project at Carnegie-Mellon University, Pittsburgh, Pennsylvania, in efforts (1) to develop efficient, portable software tools for large-scale systems simulation modeling of the nervous system and (2) to integrate broad-scale computational models, from subcellular to whole-brain levels. The international sites include Salk Institute for Biological Studies, San Diego, California; Yale University, New Haven, Connecticut; Carnegie-Mellon University, Pittsburgh; the University of Virginia, Charlottesville; the Born-Bunge Foundation, Antwerp, Belgium; and the University of Edinburgh, Scotland.

The investigators are working to develop neuroinformatics tools for data presentation, analysis, integration and synthesis

modeling, and electronic collaboration. To meet this daunting challenge, they use the NEOSIM framework, which is based on a parallel, discrete event-simulation technique, using simulation components distributed across parallel processors at the Pittsburgh Supercomputing Center, with communications via time-stamped events. The NEOSIM kernel provides mechanisms that coordinate a variety of plug-in simulation, visualization, and input/output modules. The results of this international collaborative project, which relies on well-integrated neuroscience and neuroinformatics components, are directed toward developing a virtual-reality, machine-language (VRML), parallel-simulation model of the cerebellar cortex.

The NIMH Office on Neuroinformatics, the National Institute on Aging, NCI, NINDS, and NSF contributed toward 5 years of funding to the University of Texas Health Science Center, San Antonio, to support training at the annual international meetings of the Organization for Human Brain Mapping (OHBM), a not-for-profit foundation chartered in 1995. The mission of OHBM is to promote the field of structural and functional brain mapping, emphasizing noninvasive, image-based investigation of the functional organization of the human brain. The key organizers for the OHBM meeting are the Intramural Program, NIMH; Northwestern University, Evanston, Illinois; the University of Texas Health Science Center, San Antonio; and the United Kingdom. Past annual meetings (1996–2000) were held in Canada, Denmark, France, Germany, and the United States. The next meetings are planned for Brighton, England, in 2001, and Sendai, Japan, in 2002. The general plan is to have the meeting alternate between the United States and a country outside the United States every other year. Funding is used for student stipends. The purposes of this meeting are to cooperate in the use of neuroinformatics tools to address, on a global basis, the structure and function of the human brain, in both health and disease; to present the latest advances in neuroinformatics methods for image acquisition, analysis, and meta-analysis; and to present an educational program on methods used to study the brain, with emphasis on image analysis.

### *International Meetings*

Staff from the Office on Neuroinformatics, NIMH, gave presentations on the aims and goals of the Human Brain Project/Neuroinformatics Program, a broadly based research initiative sponsored by 15 Federal organizations from four Federal agencies and coordinated by NIMH. These presentations included the following:

- International Cooperation from Agency to Investigator, as part of the program on Operational Digital Brain Atlases and Their International Cooperation, at the 20<sup>th</sup> European Winter Conference on Brain Research, in Villars Sur Ollon, Switzerland, in March 2000, and

- The Human Brain Project: Neuroinformatics, in the program on Recent Trends in Bioinformatics, at the 17<sup>th</sup> International CODATA (Committee on Data for Science and Technology) Conference, in Baveno, Italy, in October 2000.

In addition, staff of the Office on Neuroinformatics participated in the Round Table on Biological Informatics, Neuroinformatics, and Biodiversity Informatics, at the 1<sup>st</sup> International Exhibition and Congress on Biotechnology, in Genoa, Italy, in May 2000.

Staff of the Office on Neuroinformatics also met with the Minister of Science, in Rome, Italy, and with Norwegian governmental officials who are in charge of the new Fornebu Information Technology project, in Oslo. Both briefings focused on the Neuroinformatics activities of the Human Brain Project in the United States, as well as the aims and goals of OECD's Global Science Forum-Neuroinformatics Working Group.

### **Division of Mental Disorders, Behavioral Research, and AIDS**

The Division of Mental Disorders, Behavioral Research, and AIDS supports international research and research training related to behavioral, developmental, and epidemiologic studies and development of interventions. These research efforts focus on the causes, prevention, and treatment of mental and behavioral disorders and HIV/AIDS. The Division's programs discussed in this chapter are related to the Adult Psychopathology and Prevention Research Branch; the Developmental Psychopathology and Prevention Research Branch; and the Center for Mental

Health Research on AIDS (see the section on “Highlights of Recent Scientific Advances Resulting From International Activities”).

### *Psychopathology and Prevention Research*

In both developed and developing countries, mental illness and life-threatening behaviors have a grave impact on the daily quality of life of millions of individuals and their families and result in extraordinary social and economic costs due to lost productivity and increased use of medical and welfare services. The public health importance of mental illness has been slow to be acknowledged, and efforts to address mental illness as a priority are often dismissed. However, an examination of the global distribution of health burdens reveals that mental health problems account for 8.1% of lost years of quality life, which is almost twice that for heart disease and almost two and one-half times that for malaria. Behavior-related illnesses account for a staggering 34% of lost years of quality life.

There is increasing recognition of the hundreds of millions of men, women, and children who have mental illness and of the need for international agencies and ministries of health to address this public health problem. Recently, as Dr. Gro Harlem Brundtland assumed the position of Director-General of WHO, she declared that mental illness would be one of her programmatic priorities. Another example is the engagement of a mental health consultant by the World Bank.

### *Adult Psychopathology and Prevention Research Branch*

The Adult Psychopathology and Prevention Research Branch supports several international projects that will help to determine why and how mental diseases develop. When do life events such as birth complications, social stress, and trauma result in mental illness? What is the long-term outcome of serious brain disorders if treatment is begun as soon as the first symptoms appear? Does mental illness occur at the same rate in countries outside the United States? These are some of the questions addressed by NIMH’s researchers in adult psychopathology and prevention.

### *China*

China has the highest suicide rate in the world—three times higher than that in other countries. To understand this phenomenon, teams of researchers from Buffalo State College, New York, and Dalian Medical University, China, are conducting interviews with close relatives of 65 persons aged 15–49 years who recently committed suicide and comparable interviews with 65 normal control subjects matched for age and gender. Interviews will include assessments of psychiatric symptoms, suicide intent, life events, social support, and other factors of potential relevance to the Chinese culture. This study will provide preliminary data that indicate the social and cross-cultural significance of suicide in China and how best to develop and implement suicide prevention strategies for the Chinese population.

### *Czech Republic*

An investigator from Iowa State University, Ames, is conducting a longitudinal study of the effect of the post-Communism transformation on the well-being of families and individuals in the Czech Republic, as indicated by reports of physical health, emotional distress, and behavioral problems. The investigator is also examining the role of such factors as economic and job appraisal, family and social support, and psychological states in the relationship between transformation from Communism and well-being.

### *Denmark*

Using the Department of Psychiatric Demography data systems in Denmark, a scientist from Johns Hopkins University, Baltimore, Maryland, is analyzing the relationship between pregnancy and birth complications and the later development of mental disorders. The first goal of this study is to assess the relationship of pregnancy and birth complications to the psychiatric history of the mother (40,000 mothers of 600,000 giving birth). The second goal is to assess the effect of pregnancy and birth complications on the child’s later hospitalization for mental disorders.

In a separate study, researchers from the University of Southern California, Los Angeles, are investigating 9,125 consecutive deliveries in Denmark, to determine whether brain damage or the disruption of fetal neural development leads to schizophrenia. The

University of Southern California is studying Schizophrenia in High-Risk Populations, with use of a two-hit working model to guide this research. The first hit consists of a disruption of fetal neural development induced by genetic or teratogenic factors. The second hit may take the form of brain damage caused by delivery complications or stressful, nonoptimal circumstances related to child rearing.

### *Israel*

Recent animal and human studies suggest that mental stress damages the brain. An NIMH-supported study by investigators at Hadassah University Hospital, Jerusalem, measures brain structures in the same individuals before or immediately after a traumatic event and again after the development of post-traumatic stress disorder (PTSD). In an earlier study, these investigators found that, at 1 week and 6 months after a traumatic event, brain structure in survivors who developed PTSD did not differ from that in survivors who did not develop this disorder. However, damage to the brain structure may take more than 6 months to develop. The main goal of this study is to extend the follow-up period of the previous study by reevaluating brain structure at 4 years after the traumatic event and comparing these measurements with those obtained at 1 week. Demonstrating progressive damage to the brain in individuals with PTSD could have important implications for understanding the disorder and for interventions aimed at preventing its transformation into a chronic, unremitting condition. Demonstrating preexisting neuroanatomic risk factors could help to identify individuals at high risk for developing PTSD, who could be targeted for preventive interventions.

In a study of a large Israeli birth cohort, researchers from the New York State Psychiatric Institute, New York City, are examining the relationships among prenatal exposures, obstetric complications, neonatal health, heredity, and schizophrenia. They are analyzing prospective data from the Jerusalem Perinatal Study, which were obtained early in gestation in 92,000 pregnancies in Jerusalem during 1966–1974. The purpose of the study is to explore whether the incidence of schizophrenia is associated with prenatal exposures to infections, nutritional deficiencies, hormones, stress, tobacco,

anemia, vaginal bleeding, x rays, Rh incompatibility, and obstetric complications in the mother.

#### *The Netherlands*

An NIMH Scientist Development Award for Clinicians is enabling a scientist from the New York State Psychiatric Institute, New York City, to develop expertise in epidemiology, neurobiology, and neurodevelopment, so that he can independently conduct epidemiologic investigations of schizophrenia and prenatal exposures to viruses and other factors. The research plan includes an extension of a study of influenza in pregnant women and schizophrenia in their offspring, in the Netherlands. The scientist is examining whether the effect of prenatal influenza exposure on development of schizophrenia in later life is modified by an urban or a rural setting.

#### *New Zealand*

Investigators from the University of Wisconsin, Madison, are performing follow-up on 1,000 men and women, to age 26 years, in New Zealand. The goal of this project is to build a knowledge base about partner violence among young adults, the peak risk group. Results from this research will be compared with findings in a study in Pittsburgh, Pennsylvania, which is performing follow-up on a total of 500 black men and white men aged 24 years who live in urban areas. By comparing results across genders, races, and sites in two different nations, the investigators aim to determine which findings about violence in young adult partners should be used to shape theory, practice, and policy.

#### *Philippines*

In Luzon, the largest of the Philippine islands, a researcher from Johns Hopkins Bayview Medical Center, Baltimore, Maryland, is conducting an ethnographic mental health study focusing on mood and anxiety symptoms and disorders. Approximately 75 adults will be interviewed, including patients with medical and psychiatric diagnoses, control subjects from the community, and a variety of health care providers. Using information from the ethnography, the researcher will (1) describe how Filipinos experience and express mental distress and illness; (2) describe how Filipinos explain

the cause, classification, and treatment of mental distress and illness; and (3) create a dictionary of mental health terms used by Filipinos. In addition, an epidemiologic study will involve administration of a structured interview to adult patients with psychiatric diagnoses and to a representative community sample of adults. Two goals of the epidemiologic study are (1) to assess the reliability, validity, and cross-cultural applicability of methods used in the Philippines to treat mood and anxiety disorders and (2) to develop modifications that might increase reliability and validity.

#### *Scandinavia*

A senior researcher from Yale University, New Haven, Connecticut, is studying whether the vulnerability to psychosis leads to a neurobiological deterioration in early adulthood, which in turn leads to chronic disease later in life. Evidence suggests that this process may be truncated by early treatment soon after or even before onset of the deterioration. Consequently, this scientist initiated the Early Detection and Intervention in Schizophrenia study. Begun in 1997, this 4-year Scandinavian project tests whether public education about the early signs of psychosis can reduce the duration of untreated psychosis in the first episode of schizophrenia and whether such a reduction can delay the progress of the disorder.

#### *Turkey*

NIMH has funded a student at Case Western Reserve University, Cleveland, Ohio, to work on a dissertation based on an ethnographic study of religious healing among labor migrants in the Altina—aH squatter settlement of Ankara. Anthropological research has suggested that religious healing plays an important role both as a mental health care resource and in the process of transforming one's social identities and rules. The overall objective of the study is to understand the complex relationships among migration, social identities, and religious healing within one community.

#### *Ukraine*

Researchers from the State University of New York, Stony Brook, will obtain nationally representative data for Ukraine, to study the prevalence of alcoholism, substance abuse, and mental illness, as well as impairment,

disability, and availability and adequacy of treatment. The recent major societal changes in Ukraine present a unique opportunity to explore the relationships between social stress and disruption and the occurrence of mental illness.

#### *Developmental Psychopathology and Prevention Research Branch*

International research allows investigators to explore historical situations and special populations that do not exist in the United States. Unique situations in Bosnia and South Africa allow study of the effect of violence and trauma on mental health, and unique populations in Australia and Hungary that have had follow-up for many years allow researchers to study the progression of depression over time and from one generation to the next.

#### *Australia*

Researchers from Emory University, Atlanta, Georgia, have performed follow-up on a group of pregnant woman and their children in Australia for 15–20 years. In particular, they have monitored depression in the mothers and the mental health of the children. A follow-up study of these young adults at ages 15–20 years and their mothers is expected to show the effect of maternal depression on the intergenerational transmission of depression.

#### *Bosnia*

A scientist from Harvard University, Boston, Massachusetts, is working with scientists at the University of Zagreb, Croatia, to conduct the first large-scale, general population study of the role of personal, environmental, and other risk factors in modification of the relationships among three factors: trauma, psychiatric symptoms, and functional status. The study will produce the first psychiatric data from follow-up of a refugee population that allows examination of (a) dose–effect relationships among the three factors and (b) the ability to engage in economic activity before and after repatriation. A model of the impact of trauma on populations over time also will be developed.

The proposed research fills a major gap in understanding the effect of trauma on a person's ability to function and to participate in economic activity: the scientists will analyze the duration and character of the

dose–effect relationship. The design is a prospective cohort study in two time periods. Data on a cohort of 536 Bosnian refugees, obtained in 1996, will be analyzed to establish baseline estimates of trauma, symptoms, functional status, and ability to participate in income-generating activities. Cohort members will be re-interviewed after repatriation, allowing prospective assessment of the psychiatric and functional outcomes of trauma. A standardized personal interview will be administered by using previously validated questionnaires to obtain retrospective reports of trauma, contemporaneous reports of trauma experienced during repatriation, and replicate measures of depression, PTSD, and functional outcomes. Concurrent measures of personal and environmental characteristics also will be obtained, along with measures of income-generating activity. These measures will be used (1) to assess change in the dose–effect relationship of trauma to mental and physical health outcomes and (2) to test hypotheses derived from a conceptual model of the interaction between trauma and its psychiatric and functional outcomes over time.

#### *Hungary*

A longitudinal follow-up study of childhood-onset depressive disorders, at the University of Pittsburgh, Pennsylvania, was in its 9<sup>th</sup> year in FY 00. Because all children in the study will soon reach adolescence, it will be possible to observe the transition of a large subgroup of these children into adulthood. One aim of the research is to refine the classification of developmental psychopathology, with a particular focus on the practical consequences of early-onset disorders. This study is the first of its kind to perform follow-up on children with affective disorders into adulthood. It is expected that the research will contribute to improved classification of these disorders. It also will shed further light on the developmental consequences of early-onset pathology. All these goals have relevance to early identification, prevention, and treatment or remediation of these depressive disorders.

#### *Kenya*

NIMH provided funding to a team of U.S. investigators from the School of Medicine, Washington University, St. Louis, Missouri, to study survivors of the bombing of the

U.S. embassy in Nairobi, in August 1998. The researchers conducted a cross-cultural investigation of disasters, through comparison of this bombing with the bombing in Oklahoma City, Oklahoma, in 1995. Both bombings were devastating events of extraordinary magnitude, but they provided unique opportunities to study the mental health consequences for victims and their responses to such events.

In the Nairobi bombing, approximately 250 people were killed and 5,000 were injured. Despite historically frequent trauma in Nairobi, mental health professionals have not been well trained in post-trauma work, and the infrastructure for emergency response is limited. In the immediate aftermath of the embassy bombing, Kenyan mental health professionals began to organize, provide services, and collect data. With additional support from NIMH, the U.S. investigators partnered with a group of physicians representing the Kenya Medical Association to perform the following functions:

- document the extent and nature of diagnosable psychopathology in direct victims of the blast, and compare results with findings from research on victims of the 1995 Oklahoma City bombing;

- assess needs of community populations at risk for bomb-related psychosocial problems;

- provide technical assistance and training to professionals in Nairobi who have begun to gather data, to enhance the clinical and scientific sophistication of mental health interventions and their evaluation for effectiveness; and

- further develop a database to inform interventions in the aftermath of future terrorist incidents worldwide.

■ The U.S.-Kenyan investigative team has collected data on diagnosable psychiatric disorders; disability and functioning in a number of domains (e.g., family, work, and school); health status; treatment history; and physiological assessments, for approximately 95 U.S. citizens and more than 100 Kenyans working for the United States in the foreign service. The investigators also have collected data on a large number of Kenyan volunteer rescue personnel. Finally, they are obtaining data on several hundred 11- to 12-year-olds from the community.

#### *Mexico*

The goal of one cross-cultural study in Mexico, by researchers at the University of Georgia and the University of Guadalajara, is to collect postdisaster data that are comparable to the data collected in the United States after Hurricane Andrew. In data collection and analysis, the researchers will differentiate among types of resources available to the disaster victims that are presumed to mediate the relationship between trauma exposure and psychiatric outcomes. These resources include those that are impervious to the effects of trauma, such as social class; resources that are damaged by trauma, such as social, psychological, and material resources; and resources that arise in response to trauma, such as social support, coping efforts, and financial aid.

#### *New Zealand*

In 1984, the University of Wisconsin, Madison, began research on antisocial behavior among a representative New Zealand birth cohort from 1972. Existing data on this cohort, which has been interviewed at ages 3, 5, 7, 9, 11, 13, 15, 18, and 21 years, allow researchers to trace the development of antisocial behavior. This is the first longitudinal study to use neuropsychological functioning to predict the initiation and persistence of delinquent behavior. Specific hypotheses address the following questions:

- Why do some young adults persist in antisocial behavior beyond adolescence but others do not persist?

- What are the components of the broad constellation of mental disorders and life problems that accompany adult antisocial behavior?

- Can childhood aggression lead to abuse of family members in adulthood?

- Can bonds to a job or a romantic partner foster recovery from antisocial behavior?

- How does parental antisocial behavior affect children?

- Do developmental models of male antisocial behavior apply to women, or are female models needed to better understand antisocial behavior in women?

#### *Puerto Rico*

Previous studies have shown that rates of antisocial behaviors among children and adolescents are lower in Puerto Rico than

on the U.S. mainland. This study at the New York State Psychiatric Institute, New York City, compares the development of disruptive disorders and antisocial behaviors in Puerto Rican youth in the South Bronx, in New York City, New York, and in the San Juan metropolitan area, in Puerto Rico. Particular emphasis will be placed on substance use and abuse and on the role of attention-deficit hyperactivity disorder in increasing the risk for the development and persistence of antisocial behaviors.

#### *South Africa*

A team of researchers from South Africa and the United States is studying the Psychiatric Effects of Apartheid and Torture. This 5-year research project involves epidemiologists from the University of Michigan, Ann Arbor, and Harvard University School of Public Health, Cambridge, Massachusetts; the Dean of the National School of Public Health, Medical University of South Africa, Pretoria; the Chair of the Department of Psychiatry, University of the Orange Free State, Bloemfontein; and researchers at the University of Cape Town. The study will focus on 1,000 persons who testified at the hearings of the Truth and Reconciliation Commission and a random sample of 5,000 persons from all of South Africa. It will be the first study of the effects of torture on a population that will be conducted in the country in which it occurred. Other studies of the psychiatric consequences of torture have been limited to examining the effects on selected samples of the population, and these effects could not be compared with the incidence of psychiatric illness in the general population. In addition to studying the relationship between torture and mental illnesses, this study will provide the first national epidemiologic data on mental disorders in any country in Africa. The data will increase scientific knowledge and will be useful for policy development. Transformation of the health system to meet the needs of all the citizens of South Africa is a major goal of the new South African government.

### **Division of Neuroscience and Basic Behavioral Science**

#### *Behavioral and Integrative Neuroscience Research Branch*

##### *Research Grants*

Investigators at Ponce School of Medicine, Puerto Rico, are working to apply a model for the neural basis of emotional learning to control of the fear response. Lesioning (selective inactivation or destruction of tissue) and unit recording (recording of electrical activity of individual nerve cells) are being used to elucidate how the process of controlling a response may be linked to the connectivity between the medial prefrontal cortex and the basolateral amygdala of the brain. Extinction of the conditioned response of fear, which is virtually unexplored, is important because perseveration of fear is a salient feature of phobias and PTSD.

In an ongoing study of the behavioral neuroendocrinology of mating, researchers at Johns Hopkins University, Baltimore, Maryland, and the University of Liège, Belgium, are using the Japanese quail as a model in efforts to discover, at the systems level, general principles about the regulation of hormone-dependent behaviors. This model system has facilitated examination of the interrelated roles of dopamine and aromatase at the cellular level. The Belgian researchers developed the Japanese quail as a model and defined the aromatase pathway. The researchers in this study have reliably localized the protein and messenger RNA (mRNA) of brain aromatase, enabling a precise definition of the neural circuit mediating reproductive behavior. With identified circuitry in place, they are focusing on the interactions between dopamine and brain aromatase in this circuit, to specify the action of testosterone. Their study of these mechanisms is relevant to understanding the differential regulation of appetitive and consummatory aspects of motivated behavior.

Under an NIMH grant to McGill University, Montreal, Quebec, scientists are working to identify basal forebrain neuron types involved in the generation of slow-wave sleep and cortical activation associated with wakefulness and REM (rapid eye movement) sleep. The goal of the project is to identify, by the anatomic and neurotransmitter characteristics, the basal forebrain neurons re-

sponsible for the cortical activation during waking and REM sleep, as well as any that are reciprocally involved in cortical deactivation during slow-wave sleep. The scientists are investigating whether basal forebrain neurons (cholinergic, GABA-ergic, and glutamatergic cells) modulate cortical activity in a rhythmic manner during cortical activation (waking and REM sleep). Such rhythmic modulation may provide a mechanism for integrated coherent activity across cortical regions, which is observed during recording of brain activity in the sleep state.

This study is important for understanding the functional role of the basal forebrain in control of the arousal state. These findings are expected to identify, for the first time, specific neurons that are critically involved in determination of sleep-wake states and to reveal biophysical properties, neurotransmitters, and efferent projections by which these neurons modulate cerebral activity.

Investigators at McGill University, Montreal, and Boston University, Massachusetts, are using combined physiological and modeling studies to determine how acetylcholine changes cellular and network dynamics in the entorhinal cortex. Physiological data indicate that increased acetylcholine levels may support sustained activity in the entorhinal cortex, which may (a) allow buffering of novel input patterns across short intervals in delayed match to sample tasks and (b) enhance formation of memory traces in the hippocampus. In contrast, low levels of acetylcholine may set the dynamics for consolidation of additional memory traces.

In a project initiated in 1995 at College de France, Paris, researchers are studying the functional and neuronal mechanisms of interval timing and the role of the basal ganglia in timing control (internal sense of time) in patients with Parkinson's disease and normal control subjects, including a population of older adults. Some patients will be tested with and without administration of medication, and others will be tested with and without deep brain stimulation through electrodes implanted in deep brain structures of the basal ganglia, for control of symptoms of Parkinson's disease.

Investigators at Northwestern University, Chicago, Illinois, and the University of Paris and Institut National de la Recherche Agronomique, Jouy-en-Josas, France, are exploring the role of oxytocin in male sexual

function. They are evaluating unexplored neural circuitry at multiple levels of analysis including behavior, to elucidate how important pathways in the brain regulate peripheral reflexes. The investigators will also study a newly discovered direct pathway from the paraventricular nucleus to the lumbosacral spinal cord, which is a potent facilitator of penile erection. In this circuit, oxytocin acts as the neurotransmitter via a spinal nitric oxide pathway.

In a research project on the hippocampal interneuronal network, an investigator at Rutgers State University, Newark, New Jersey, is exploring the anatomy and physiology of inhibitory interneurons in the hippocampus, a brain structure that is critically involved in memory functions. The investigator is combining dual intracellular recording from functionally connected neurons in the hippocampus with intracellular staining and sophisticated, double-labeling, immunocytochemistry techniques, to reveal the connectivity patterns of hippocampal inhibitory interneurons. In this collaborative effort, the investigator at Institut Pasteur, French National Institutes of Health and Research (INSERM), Paris, France, provides unique expertise in the technique of dual intracellular recording in the hippocampus, and the investigator at the Institute of Experimental Medicine, Budapest, Hungary, is a world expert in the immunocytochemistry techniques that are being used.

Scientists at the University of California, San Diego, and Otto von Guericke University, Magdeburg, Germany, are working to determine the neural level at which attentional modulation of sensory information can be detected. They are using multiple imaging methods (event-related potential, fMRI, and magnetoencephalography) and multiple sensory systems (visual and auditory) in a systematic exploration of the neural mechanisms by which attention selection of sensory cues occurs. Mechanisms of attention are one of the core problem areas in cognitive neuroscience.

Researchers at Hebrew University, Jerusalem, Israel, are collaborating with NIMH researchers to analyze the limits that "noise" places on the precision of nerve cell firings. They are measuring several noise sources, including noise due to the random nature of ionic channels, the effect of "spontaneous" background activity, and the noise intro-

duced by the unreliable nature of synaptic transmission. The phases of the study are as follows:

1. characterization of these noise sources in brain cortical neurons by using combinations of drugs that allow isolation of the contribution of individual noise sources;

2. injection of "constant" noise into some nerve cells and recording of the noise in the next neuron in the chain, allowing computation of the mutual information transmitted between the input- and the output-spike trains (continuous, temporally linked sequences of electrical activity measuring the action potentials of individual nerve cells);

3. comparison of these measurements with analytic and numerical computer models of several types of noise in weakly active linear cables, obtained by incorporating the anatomic and physiological properties of these cells; and

4. creation of mathematical models of the relationship between noisy inputs and variable outputs of these cells and comparison with the experimental data.

This research is expected to lead to a quantitative picture of the properties of neuronal noise sources and their effect on the information capacity of individual cortical neurons.

#### *Other International Activities*

NIMH supported a workshop entitled Determinants of Vigilance: Interaction Between the Sleep and Circadian Systems, in Fort Lauderdale, Florida, on October 19–22, 1999. Research on sleep and biological rhythms is significant because sleep and circadian systems are important regulators of the brain, behavior, and mood.

NIMH contributed financial support to the 9th Annual Computational Neuroscience Meeting, in Brugge, Belgium, on July 16–20, 2000. This is the 1<sup>st</sup> year that this international meeting has been hosted in a foreign country, and the overall attendance level was the highest to date. This yearly interdisciplinary conference is organized around the broad range of research approaches and issues involved in understanding the function of nervous systems. Started in 1992, these meetings have brought together experimental and theoretical neurobiologists along with engineers, computer scientists, cognitive scientists, physicists, and mathematicians interested

in understanding the relationship between the structure and function of mammalian and nonmammalian nervous systems.

In addition, NIMH contributed financial support to the annual meeting of the Society for Behavioral Neuroendocrinology, which was held jointly with the VI<sup>th</sup> International Conference on Hormones, Brain, and Behavior, in Madrid, Spain, on August 5–9, 2000. The society made 15 travel awards for U.S. and non-U.S. student members to present original research at the meeting.

#### *International Meeting*

Recent technological innovations are making dynamic (time-varying) brain imaging a reality. The meeting on Dynamical Neuroscience VII: Integration Across Multiple Imaging Modalities, which was supported by NIMH, was held in Delray Beach, Florida, on October 21–22, 1999. This symposium, which was funded by NIMH, surveyed the latest brain-imaging techniques and addressed the issue of how data on several scales of space and time may be combined to obtain a deeper understanding of the brain in health and disease. International invited speakers addressed the following topics: from McGill University, Montreal, on Integration of Transcranial Magnetic Stimulation and Brain Imaging; from University College, London, England, on (1) Scanning Patients With Tasks They Can Perform and (2) Context-Sensitive and Nonlinear Brain Responses Measured With fMRI; from Helsinki University of Technology, Espoo, Finland, on Brain Mechanisms of Action Viewing: a Neuromagnetic Approach; and from Max Planck Institut for Biological Cybernetics, Tübingen, Germany, on Functional Magnetic Resonance Imaging in Monkeys.

#### *Behavioral Science Research Branch*

##### *Research Grants*

NIMH is supporting a researcher at the University of New Mexico, Albuquerque, and researchers at Universidade Estadual do Norte Fluminense, Rio de Janeiro, Brazil, to study foraging and eating behavior in the golden lion tamarin monkey. The goal of the research is to understand how food acquisition behavior develops in young tamarins, as a function of the interplay between trial and error and social learning from parents and other adults. Two behav-

ioral–observational studies are being conducted, one in the field at the Poco das Antas Reserve, outside Rio de Janeiro, and one with a captive population at Centro de Primatologia do Rio de Janeiro. In addition to its significance in basic science, this research has relevance to the development of human eating disorders, because this primate species resembles humans in the way that the development of eating behavior is shaped under social control.

An NIMH investigator-initiated research grant to the University of Colorado for study of the developmental behavioral genetics of transition into early adolescence includes a subcontract to the Institute of Psychiatry, University of London, England. By integrating longitudinal data sets, one on twins and one on adopted persons, this work is expected to yield accurate estimates of genetic and environmental influences on cognitive, socioemotional, and related aspects of children's development during the transition from childhood to adolescence. Because the data sets include information on a broad range of developmental factors, including cognitive, reading, behavioral, and health-related variables, the findings are substantially increasing knowledge about genetic and environmental contributions to normal and abnormal development in childhood and adolescence. Since 1977, more than 150 reports and several books have been published on data supported by the NIMH grant. The NIMH support has been essential to this research, which is widely recognized to be a landmark study of developmental behavioral genetics.

An investigator at Indiana University, Bloomington, is engaged in a study of children in the United States and Japan, to develop and test a theory of how children aged 20–36 months learn the grammatical properties and meanings of nouns. The investigator is working with nurseries and parenting groups in the area of Niigata, Japan. There are significant differences between the English and Japanese languages in the grammatical properties of subclasses of nouns with particular types of meanings, such as nouns for inanimate objects, substances, animate objects, animals, and people. Thus, comparing acquisition of English and Japanese nouns can lead to a broader, more adequate account of language acquisition, including identification of the most funda-

mental underlying processes. In addition to experiments with children, the research in both the United States and Japan includes studies of the speech that parents direct to their children and statistical analyses of the frequencies of different types of nouns across contexts in everyday discourse. Ultimately, a computational model of the acquisition of noun knowledge will be developed.

Scientists at Washington University, St. Louis, Missouri, Osaka City University, Japan, and the University of Warsaw, Poland, are collaborating to investigate the cognitive processes that underlie reward discounting in both humans and animals and to test the generality of results obtained in the United States. Discounting is the reduction in subjective value of a reward (any type of positive outcome) if that reward is delayed or if its probability is reduced. Individual differences in discounting processes may help to explain addictions, impulsivity, risk taking, and treatment compliance. Some of the studies in Poland took advantage of the changeover from an inflationary currency to a noninflationary currency, to study discounting in quasi-naturalistic monetary situations. Preliminary results indicate that the same basic mechanisms underlie discounting in people in Japan, Poland, and the United States, thus strengthening the claim that discounting in humans, as well as in animals, is the consequence of fundamental and universal cognitive mechanisms. The findings suggest that culture or experience affect the parameter settings rather than the overall form of the mechanisms.

An NIMH-supported scientist at the University of Texas, Austin, is collaborating with scientists at Auckland Medical School, New Zealand, in research on interpersonal disclosure processes and health. Previous work by the U.S. scientist showed that writing about upsetting emotional experiences is associated with long-term improvements in mental and physical health, such as lower rates of depressive symptoms, fewer adjustment difficulties, and reduction of common illnesses and physical symptoms. The goal of the research is to understand the mechanisms and pathways by which the beneficial effects of the “disclosive” writing paradigm occurs and which individuals are most likely to benefit from this process. The scientists are using in-depth language analysis in both

naturalistic and laboratory studies to investigate the role of potential intra-individual psychological and social process mechanisms. The research also examines physiological processes, social processes, and more stable personality correlates of this phenomenon.

#### *Clinical Neuroscience Research Branch Research Grant*

An investigative team at Karolinska Institute, Stockholm, Sweden, is conducting research on dopamine receptors in patients with schizophrenia, concentrating on the D<sub>1</sub> receptor, which is thought to have a major role in the regulation of short-term memory. These scientists are considered to be international leaders in the development of novel ligands (biological markers) for use in PET imaging. They are using this skill to study the several classes of dopamine receptors in patients with schizophrenia. In complementary experiments to measure mRNA for dopamine receptors, the scientists are performing postmortem examination of brains of patients with schizophrenia and control subjects. Such studies will help to define the exact differences in the schizophrenic brain and could lead to an enhanced understanding of the disorder's pathophysiology and to new therapeutic possibilities.

#### *Genetics Research Branch Research Grants*

Several large-scale human genetics projects funded by NIMH in FY 00 include international activities. These projects are expected to greatly complement ongoing NIMH-funded human genetics projects that analyze pedigrees collected in the United States to identify genes conferring vulnerability to mental disorders.

Researchers at the University of Costa Rica, San José, and at Instituto de Información e Investigación en Salud Mental, Monterrey, and Grupo de Estudios Médicos y Familiares Carracci, Mexico City, Mexico, are working in a two-site collaborative project on the genetics of schizophrenia. The researchers are obtaining comprehensive clinical information and DNA samples from families of Latino descent across the southwest United States, southern California, Mexico, and Central America. This large-scale collaborative project includes numer-

ous researchers in Central and South America, and it is expected to yield the largest data set collected to date on Latin Americans affected with schizophrenia.

In another study, investigators at the University of Costa Rica, San José, are recruiting a sample of patients with schizophrenia who are descended from the founder population in Costa Rica. The Costa Rican population is ideal for this study, because it is a large population descended over 20 generations from a small group of founders. The investigators are using linkage disequilibrium methods to evaluate patients and their parents, to map genes that produce vulnerability to schizophrenia.

An award was made to the London School of Hygiene and Tropical Medicine, England, to collaborate with the Biostatistics Unit, Medical Research Council, Cambridge, England, and Penn State University, to develop statistical methods and markers for mapping genes that confer vulnerability to complex diseases. The work is based on a novel approach that exploits the correlation of ancestry on chromosomes found in ethnically admixed populations.

An international collaborative research team, consisting of investigators at Centre Nationale de la Recherche Scientifique, Paris, France, the University of Bonn, Germany, and the University of Wales, Cardiff, is undertaking genetic studies of candidate regions of chromosomes that may carry susceptibility to schizophrenia. The team is examining eight samples of pedigrees collected in France, Germany, the United Kingdom, and the United States. This large international study will permit assembly of a data set of nearly 900 pedigrees—the largest data set studied to date in the search for genes producing vulnerability to schizophrenia.

Scientists at the Kosrae Department of Health Services, Tofol, Kosrae, and the Yap Department of Health Services, Colonia, Yap, Micronesia, and the University of Pretoria and Weskoppies Hospital, Pretoria, South Africa, are recruiting families affected with schizophrenia from the island populations of Kosrae and Yap and the Afrikaners in South Africa. These genetically isolated populations offer excellent genealogical data that will significantly improve the ability to conduct genetic analyses on schizophrenia by taking into account all known genealogical relationships.

### *Molecular and Cellular Neuroscience Research Branch*

#### *Research Grants*

The Psychopharmacology Program in the Molecular and Cellular Neuroscience Research Branch supports two research projects. In these studies, an investigator at McGill University, Montreal, has a central role in applying his model of maternal separation in rats to examine the effects of early postnatal experience on behavioral, neuroendocrine, and neurochemical responses to stress in adulthood. In the first study, he is examining the influence of postnatal maternal separation on susceptibility to adverse effects of stress in adult rats. In the second study, he is exploring the effects of natural variations in maternal behavior on the development of behavioral responses to stress, on patterns of maternal behavior in offspring, and on the interrelatedness of behavioral, hormonal, and neurochemical changes.

Recent studies revealed potent effects of maternal separation on molecules regulating stress responses in the brain, including increased release of norepinephrine and higher levels of 5HT<sub>2A</sub> serotonin receptors in the medial prefrontal cortex. Separation of rat pups for a short duration induced an increase in maternal behavior and the expression of a GABA-A receptor subunit that confers high affinity for ( $\gamma$ -aminobutyric acid (GABA) in brain regions that regulate emotion (amygdala, prefrontal cortex, and locus caeruleus). The rats with maternal separation had lower GABA-A receptor expression in these brain regions. These data suggest that early experience regulates the expression and composition of the anxiety-modulating GABA-A receptors and, hence, receptor responsiveness within restricted brain regions. In a separate study, the offspring of mother rats exhibiting high levels of maternal behaviors showed increased expression of mRNA for an NMDA receptor subunit and for brain-derived neurotrophic factor, as well as increased cholinergic innervation of the hippocampus and enhanced spatial learning and memory.

Results of these studies reveal that maternal care in infancy profoundly affects the development of brain systems regulating behavioral, endocrine, and autonomic responses in adulthood.

The Neuropharmacology Program of the

Molecular and Cellular Neuroscience Research Branch supports a researcher at the National Institute of Mental Health and Neuroscience, Bangalore, to study the metabolism of psychoactive drugs by the brain enzymes cytochromes P-450. The goals of the research are (1) to determine the capability of human brain cytochromes P-450 to metabolize psychoactive drugs and (2) to characterize and localize the multiple forms of the P-450 enzymes in human brain. The novel hypothesis is that enzymatic activity in specific brain regions may be important in modulating the concentration and duration of action of drugs at their primary sites of action in the brain. The psychoactive drugs being studied include fluoxetine (Prozac), haloperidol (Haldol), clomipramine (Anafranil), and diazepam (Valium)—drugs used clinically to treat depression, obsessive-compulsive disorder, schizophrenia, and anxiety disorders. These studies are important for understanding how the human brain metabolizes psychoactive drugs and for the development of new therapeutic interventions for neuropsychiatric disorders.

In FY 00, this researcher investigated cytochromes P-450 and associated monooxygenase activities in human brain mitochondria isolated from eight regions of four human brain samples obtained at autopsy. The study demonstrates the presence of multiple forms of P-450 in human brain mitochondria. The cytochromes belong to three subfamilies (1A, 2B, and 2E) and are involved in metabolism of drugs and other xenobiotics.

#### *International Meeting*

An NIMH-sponsored workshop, Strategies for Identifying Functional Links Between the Immune System, Brain Function, and Behavior, was held in Bethesda, Maryland, on May 23–24, 2000. The goal of the workshop was to identify promising research directions and strategies for understanding the impact of immune molecule activation on brain function and behavior. The meeting brought together 14 experts in basic science research and clinical studies in the fields of neuroimmunology, neuroendocrinology, receptor and molecular signaling, neural development, genetics, psychiatry, and behavior. A basic neuroscientist from Laval University, Quebec, discussed cytokine sig-

naling in the brain induced by systemic immune challenge.

## **Division of Services and Intervention Research**

### *Research Grants*

#### *Adult and Geriatric Treatment and Preventive Intervention Research Branch*

The Adult and Geriatric Treatment and Preventive Intervention Research Branch is funding research to determine the efficacy of the selective serotonin reuptake inhibitor, fluoxetine, in reducing the rate of relapse and in enhancing psychological and behavioral recovery after the initial treatment for anorexia nervosa. This 4-year, collaborative study will be conducted at two sites—in New York and Toronto, Ontario. A total of 80 patients with anorexia nervosa who have successfully completed initial treatment in an inpatient or intensive outpatient program will be randomly assigned to receive fluoxetine or placebo for 12 months under double-blind conditions, while receiving appropriate psychological treatment. Outcome will be assessed on the basis of maintenance of weight and reduction in psychopathological symptoms characteristic of this condition.

Anorexia nervosa is a serious psychiatric disorder with substantial morbidity and a lifetime similar to that associated with any psychiatric illness. A major contributor to the poor prognosis of this illness is the high rate of relapse that follows successful initial treatment. Patients with anorexia nervosa often exhibit symptoms of other psychiatric disorders, such as major depression and obsessive-compulsive disorder, which respond favorably to treatment with medication. It is surprising therefore that medication treatment for this disorder has been consistently unsuccessful. Virtually all of the controlled trials of medication have been conducted during the initial phase of treatment, when patients are underweight. It is possible that the usefulness of medications is limited during this phase of illness because of the physiological and neurochemical effects of starvation. Therefore, it may be useful to explore the usefulness of medication among patients with anorexia nervosa after initial treatment has reversed the acute effects of starvation.

Another study supported by the Branch will take place at Laval University, Quebec. The specific aims of this study of behavioral

and pharmacological treatment for insomnia are (1) to evaluate the short- and long-term effects of cognitive-behavioral therapy (CBT) alone and in combination with medication, for chronic insomnia, (2) to compare the efficacy of various maintenance strategies for combining drug and nondrug therapies to optimize long-term outcomes, and (3) to examine the clinical impact of treatment on daytime functioning and psychological well-being. In this study, 150 adults meeting criteria for chronic insomnia will be randomly assigned to receive CBT or CBT plus medication. Therapy will consist of an initial treatment phase of 8 weeks, followed by an extended treatment phase lasting 6 months. Outcome will be evaluated across measures of sleep, clinical ratings, and several indices of daytime functioning. The measures will be administered at baseline, at the end of the initial and extended treatment phases, and at 6-, 12-, and 24-month follow-ups.

The main research questions are as follows:

1. Is CBT in conjunction with medication more effective than CBT alone for the initial treatment of insomnia?

2. When combining CBT and drug therapy, is it best to discontinue medication after the initial treatment or to continue using it on an intermittent (as needed) schedule, to foster long-term maintenance of sleep improvements?

3. What is the clinical impact of sleep improvement on daytime fatigue and performance, psychological symptoms, and quality of life?

Insomnia is a prevalent health complaint that is often associated with functional impairments, reduced quality of life, and increased health care costs. The public health significance of the proposed study is that it will provide useful information about optimal models for integrating behavioral and pharmacological therapies for the clinical management of insomnia.

Also at Laval University, the Branch is funding a study on insomnia in late life and long-term use of benzodiazepines. The purpose of this research is to evaluate the efficacy of CBT and supervised tapering of medication, alone and in combination, for discontinuation of benzodiazepine in persons with insomnia who are dependent on hypnotic medication. A total of 75 adults older than 60 years who meet criteria for

dependency on hypnotic medication for treatment of insomnia will be randomly assigned to one of three treatment conditions: (1) CBT combined with supervised tapering of medication; (2) tapering of medication only; or (3) CBT only. All three interventions will last 10 weeks after the initial 2-week baseline period. Follow-ups will be conducted at 3, 12, and 24 months. Treatment outcome will be assessed across measures of sleep, mood, daytime performance, and quality of life. The main research questions are as follows:

1. Which of three treatment modalities is most effective for discontinuation of benzodiazepine and improving sleep patterns among persons with insomnia and dependency on hypnotic medication?

2. What are the short- and long-term effects of discontinuation of hypnotic drugs on sleep, daytime performance, mood, and quality of life of older adults with insomnia?

3. Are there predictors (e.g., chronic insomnia, duration of use of hypnotic medication, and coping styles) of successful outcome (i.e., freedom from drug use, improved sleep, or both).

The long-term objectives of this study are to further the understanding of insomnia and long-term use of benzodiazepines in late life and to design an effective treatment program that could be implemented routinely in the clinical management of insomnia with dependency on hypnotic medication.

Insomnia is a prevalent health problem in late life and its treatment is predominantly pharmacological. Of patients who are prescribed a hypnotic medication, 10%–15% continue to use it for more than 1 year, despite evidence that long-term use is ineffective and detrimental to health and quality of life. It is primarily older adults who prolong use of hypnotic medications. Although psychological (cognitive-behavioral) interventions have been used successfully in persons with insomnia who do not take medication, there is little empirical data on the efficacy of such nonpharmacological interventions for insomnia with dependency on hypnotic agents.

#### *Child and Adolescent Treatment and Preventive Interventions Research Branch*

The Child and Adolescent Treatment and Preventive Interventions Research Branch is funding a study to continue the NIMH col-

laborative Multimodal Treatment Study of Children With Attention Deficit Hyperactivity Disorder (ADHD). In a parallel group design, 579 children aged 7–9 years with a diagnosis of ADHD, according to rigorous standards, were randomly assigned to one of four conditions: (1) medication only, (2) psychosocial intervention only, (3) combined (medication and psychosocial) intervention, and (4) assessment and referral. All children but those with assessment and referral were treated intensively for 14 months, and assessments for all subjects were performed at baseline and 3, 9, 14, and 24 months later. Additional funding in the future will support recruitment of a local normative comparison group drawn from the schools attended by the children with ADHD. This continuation would extend the follow-up to assessments at 36, 60, and 84 months after treatment.

The aims of continuing the study are as follows:

1. to track the persistence of intervention-related effects as the children in the study sample mature into mid-adolescence, including subsequent patterns of use of mental health–related and school-related services as a function of treatment group and outcome (level of treatment success at 14 months after treatment);

2. to test specific hypotheses about predictors, mediators, and moderators of long-term outcome among children with ADHD (e.g., comorbidity, family functioning, cognitive skills, and peer relations) that may influence adolescent functioning, either independently of or through initial treatment assignment, treatment outcomes at 14 months, or both factors, and to compare how these predictors and moderators are similar or dissimilar within the local normative comparison group;

3. to track the patterns of risk and protective factors (including their mediation or moderation by initial treatment assignment, outcome, or both) that are involved in early and subsequent stages of developing substance-related disorders and antisocial behavior; and

4. to examine the effect of initial treatment assignment and degree of treatment success on later academic performance, achievement, school conduct, tendency to drop out of school, and other adverse school outcomes.

The Branch also supports a research pro-

ject on one-session treatment for specific phobias in children and adolescents. The overall aim of this grant is to examine the efficacy of a cognitive–behavioral treatment in reducing symptoms and sequela of specific phobias. Findings indicate that clinically significant specific phobias are present in approximately 5% of children in community samples and in about 15%–20% of children presenting at clinics for phobia and anxiety disorders. Furthermore, findings indicate that children referred to clinics who present with specific phobias in specialized clinics are likely to also have other anxiety disorders, affective disorders, and disruptive-behavior disorders. For many children, the phobia results in considerable academic, social, and personal distress, as well as interference in day-to-day activities. Phobias may persist for a lifetime.

One-session treatment has been found to be a rapid and effective therapy for adults with phobic disorders. Surprisingly, this treatment has not been evaluated in countries other than Sweden, and its usefulness in the treatment of childhood phobias has not been examined. A systematic evaluation of its efficacy in Virginia and Sweden is proposed.

Specific aims are threefold: (1) to evaluate the efficacy of one-session treatment with children in a controlled, randomized trial; (2) to undertake systematic evaluation of its efficacy in Virginia and Sweden; and (3) to explore predictors of treatment outcome, including parental psychopathology, overinvolved parenting styles, and the presence of other disorders in the child. In this study, 120 children (60 boys and 60 girls) in Virginia and 120 children (60 boys and 60 girls) in Sweden between 8 and 14 years of age who meet the criteria of the *Diagnostic and Statistical Manual of Mental Disorders, 4<sup>th</sup> edition (DSM-IV)*, for a primary diagnosis of specific phobia will be randomly assigned to receive one-session treatment or education and support or as control subjects on a waiting list. After a specified period, children in the waiting-list control group and in the education and support group who still meet criteria for a specific phobia will receive one-session treatment. Depending on remission and attrition rates, this strategy will permit a relatively robust examination of the efficacy of one-session treatment, its systemat-

ic evaluation in Virginia and Sweden, and the predictors of treatment outcome.

Thus the investigation will build on strengths in the current literature by using cognitive–behavioral procedures that have some, albeit limited, support in the treatment of children with phobias. At the same time, it will address shortcomings in extant studies by examining a treatment that has not been previously studied in children and by examining the role of parental psychopathology, parental overprotectiveness, and the presence of other disorders in the child in moderating treatment outcome. There is considerable support for one-session treatment for a specific phobia in adults.

#### *Services Research and Clinical Epidemiology Research Branch*

The Services Research and Clinical Epidemiology Research Branch is supporting a randomized trial of a multicomponent intervention program to improve detection and management of depression among women in primary care. This study will be conducted in three public primary care clinics in deprived areas of Santiago, Chile. Using a two-stage screening process, consecutive women with current depressive disorders who seek primary care will be identified and invited to participate. Baseline assessment will include severity of symptoms, status of diagnosis, treatment history, medical and psychiatric morbidity, substance use, and functional status and disability. Consenting patients will be randomly assigned to usual care or to a comprehensive program in which the intensity of treatment will be adjusted according to the severity of symptoms. For all patients in the intervention group, the program will include a brief, structured, group program emphasizing education, behavioral activation, and problem solving. Patients with more severe depression at the initial assessment will also be referred to the primary care physician to be evaluated for medication. All patients will be contacted for a formal assessment of treatment response after 6 weeks. Women with persistent depression will be referred to the primary care physician for an evaluation, which will focus on starting pharmacotherapy, for those not already receiving medication, or adjustments in existing pharmacotherapy. All patients receiving usual care and intervention

will complete follow-up assessments, according to a blinded procedure, at 1, 3, and 6 months after randomization. The assessments will include measurements of the severity of symptoms, functional status and disability, and use of health care. These data will be used to answer the following questions: (1) Is delivery of organized treatment for depression feasible in deprived, public-sector, primary care clinics? (2) Does the intervention program improve the clinical and functional outcome more than usual care does? (3) What are the incremental cost and cost-effectiveness of the intervention program compared with usual care?

#### *International Meetings*

The Director, Division of Services and Intervention Research, consulted with the Mental Health and Substance Abuse Department at WHO on initiatives they are planning to launch. In addition, NIMH sponsored an extramural researcher at WHO to help with development of several WHO initiatives

A representative of the Division of Services and Intervention Research made a presentation on child psychotherapy research at a meeting of the European Association in Child and Adolescent Psychiatry, in Oslo, Norway, on May 24–28, 2000, and at the 6<sup>th</sup> Annual Hellenic Bio-Medical Congress, in Athens, Greece, on October 4–8, 2000.

Another representative gave a presentation at the NIMH-sponsored meeting on the New Clinical Drug Evaluation Unit, on May 30–June 2, 2000. An NIMH staff member and a researcher from France cochaired a panel on Clinical Development of Psychotropic Drugs: Differences and Synergies Between Europe and the U.S. The panel included presentations from investigators from England and France and from regulatory officials of the U.S. Food and Drug Administration and the Medicines Control Agencies of the United Kingdom. The panel reviewed the medication and drug-development processes in the United States and Europe and discussed the advantages and disadvantages to investigators, consumers, and the pharmaceutical industry, of various approaches to development of medications and drug approval.

In Western Europe, there is an increasing interest in psychopharmacological therapy for children, and a number of informal collaborations to exchange information on

methodology in pediatric clinical trials have been started between European researchers and staff at the Child and Adolescent Treatment and Preventive Intervention Research Branch. The Chief of the Branch participated in the 12<sup>th</sup> Meeting of the Italian Society of Neuropsychopharmacology, in Cagliari, Italy, in June 2000. He spoke on multicenter clinical trials in child psychopharmacology.

Challenges for the 21<sup>st</sup> Century: Mental Health Services Research—14<sup>th</sup> Annual Conference was held in Washington, D.C., during July 2000. The conference covered a variety of topics in research on health services. Several international participants made presentations at the conference.

The Chief, Services Research and Clinical Epidemiology Research Branch, gave a presentation on Psychopharmacoepidemiology: Challenges and Opportunities, at the meeting of the International Society for Pharmacoepidemiology, in Barcelona, Spain, in the fall of 2000.

#### **Intramural Programs and Activities**

The NIMH Division of Intramural Research Programs plans and administers a comprehensive, long-term research program exploring the causes, diagnosis, prevention, and treatment of mental disorders, as well as the genetic, biological, developmental, environmental, and social factors that determine human behavior and development. The Division operates Laboratories and clinical Branches on the NIH campus in Bethesda and at the Poolesville Animal Facilities, both in Maryland. Several hundred active research projects in the basic neurosciences, clinical pharmacology, clinical psychiatry, and behavioral sciences are conducted in these facilities each year. Using a bench-to bedside approach, Division scientists provide a critical link between basic and applied research on mental disorders.

During FY 00, scientists in the Division of Intramural Research were engaged in several projects with foreign scientists. The Division offered a broad range of research opportunities for foreign scientists, including 2 Guest Researchers, 4 Staff Scientists, 20 Research Fellows, and 63 Visiting Fellows. The investigators are from Argentina, Australia, Bosnia, Brazil, Canada, China, Ethiopia, France, Germany, Hungary, India, Israel, Italy, Japan, Korea, Mexico, the Netherlands,

New Zealand, Paraguay, Slovakia, Switzerland, the United Kingdom, and Taiwan.

The Division of Intramural Research Program comprises 25 Branches and Laboratories. Selected examples of collaborative research projects are highlighted here. These joint efforts illustrate the depth and diversity of the NIMH intramural projects.

#### **Child Psychiatry Branch**

The Child Psychiatry Branch conducts clinical research that focuses on the causes, diagnosis, and treatment of psychiatric disorders with onset in childhood. International studies include the following:

- a prospective, longitudinal study of use of MRI brain scans for untreated subjects at high risk of mental illness and for control subjects (University of Melbourne, Australia);

- exploration of the use of an automated software system for analysis of anatomic MRI scans (Montreal Neurological Institute, McGill University);

- a collaborative genetic linkage study of very early onset schizophrenia (Institute of Psychiatry, London, England);

- research into childhood-onset, obsessive-compulsive disorder and tic disorders, in which 300 children aged 10–15 years and their primary caregivers are interviewed to assess neuropsychiatric symptoms, the course and periodicity of illness, and the association of the disorders with infection (Hospital Infantil de Mexico, Mexico City); and

- a study of childhood-onset schizophrenia (Karolinska Hospital, Stockholm, Sweden).

#### **Clinical Neuroscience Branch**

The Clinical Neuroscience Branch conducts basic and clinical research on the molecular, cellular, and genetic aspects of inherited disorders involving the nervous system. The Branch maintains extensive international joint efforts in basic and clinical research with 23 institutions in 15 countries. Scientists conduct international research in molecular genetics, molecular structures, and Gaucher disease.

#### *Molecular Genetics*

In molecular genetics, collaborative studies of genetic mapping and gene isolation are

being performed at the German Cancer Research Center, Heidelberg.

### ***Molecular Neurogenetics***

In molecular neurogenetics, scientists at Erasmus University, Rotterdam, the Netherlands, are collaborating on electron microscope and immunopathological studies of transgenic animal models, including lysosomal diseases such as Gaucher disease.

### ***Molecular Structures***

In the study of molecular structures, joint research is being conducted in the following areas:

- structural studies of proteins from hibernating animals (Carleton University, Ottawa, Ontario);
- structural studies of stress proteins in plants (University of Toronto, Ontario);
- structural studies of *N*-hydroxylation enzymes (University of Waterloo, Ontario);
- research on crystallizing recombinant human glucocerebrosidase (University of Pierre and Marie Curie, Paris, France);
- studies on structure and function of allergens (Indian Institute of Science, Bangalore);
- structural studies of amyloid proteins and peptides in human disease (Heller Institute of Medical Research, Tel Hashomer, Israel); and
- studies on structure and function of neurotoxins from scorpions (Universidad Nacional Autonoma, Institute of Biotechnology, Cuernavaca, Mexico).

### ***Gaucher Disease***

In the study of Gaucher disease, joint research is being performed in the following areas:

- neonatal Gaucher disease (The Adelaide Children's Hospital, North Adelaide, South Australia; Erasmus University, Rotterdam, the Netherlands; and University of Geneva, Switzerland);
- epidermal manifestations of glucocerebrosidase deficiency (University of Erlangen, Germany);
- Gaucher disease and cholelithiasis (Rambam Medical Center, Haifa, Israel);
- unusual manifestations of Gaucher disease (Gaucher Clinic, Shaare Zedek Medical Center, Jerusalem, Israel);

- correlations between genotype and phenotype (Rabin Medical Center, Tel Aviv, Israel);

- unusual presentations of type 3 Gaucher disease (Kumamoto University School of Medicine, Japan; Ajou University School of Medicine, Suwon, Korea; and Istanbul University, Turkey); and

- Gaucher disease with parkinsonian manifestations (Queen's University, Ontario; Salpêtrière Hospital, Paris, France; Semmelweis University, Budapest, Hungary; Metabolic Institute, Trieste, Italy; and Children's Memorial Health Institute, Warsaw, Poland).

### **Clinical Brain Disorders Branch**

The Clinical Brain Disorders Branch conducts research on the causes and effects of schizophrenia in the adult brain. Collaborative research projects include the following:

- studies of the pathophysiology of schizophrenia and affective disorders, with use of postmortem human brain tissue and state-of-the-art molecular biological techniques (Oxford University, England, and Genset, Paris, France);
- investigation of the genetics of schizophrenia in siblings (Free University of Berlin, Germany);
- evaluation of the effects of stress on expression of neurotrophic factors (University of Milan, Italy); and
- use of a rat model for schizophrenia to screen for novel therapeutic targets (Hoffmann-La Roche, Basel, Switzerland).

### **Other Studies**

During FY 00, many other NIMH intramural collaborative research projects yielded scientific information of significance and merit to both U.S. and foreign scientists. Projects include the following:

- The Biological Psychiatry Branch collaborated with McGill University, Montreal, on the effect of impaired function of type II glucocorticoid receptor in transgenic mice; with the University of Rome, Italy, on the neurobiology of noncompetitive NMDA antagonists; with Josai University, Saitama, Japan, on apoptosis in neurons; and with the University of Tokyo, Japan, on neuroimmune interactions.

- The Geriatric Psychiatry Branch collaborated with Oxford Glycosciences, Inc., England, on a project using two-dimensional gel electrophoresis of cerebrospinal fluid in

patients with Alzheimer's disease and healthy control subjects, to discover biological markers in the disease process.

- The Laboratory of Cellular and Molecular Regulation worked with the Weizmann Institute, Rehovot, Israel, on the structure and assembly of the acetylcholine receptor; with the University of Bergen, Norway, on functional anatomy and regulation of signal molecules by neural activity; with the University of Santander, Spain, on the regulation of neurotransmission by receptors and transporters; and with Karolinska Institute, Stockholm, on neuroimmune interactions in infectious parasitic disease.

- The Laboratory of Cerebral Metabolism collaborated with the Medical Research Council Cyclotron Unit, Hammersmith Hospital, London, England, and the PET Center, Hospital San Raffaele, Milan, Italy, on the kinetic modeling of PET radiotracers. This group also collaborated with the University of Heidelberg, Germany, to study the relationships between local densities of blood-brain barrier and brain cell glucose transporters and local cerebral utilization of glucose. (The Laboratory Chief is a permanent external member of the Max Planck Society of Germany and, in that capacity, engages in frequent exchanges of information with members of the Max Planck Institute for Neurological Research, Cologne, on methods, strategy, and results of studies on cerebral blood flow and metabolism and on techniques for use of PET and nuclear magnetic resonance imaging).

- The Laboratory of Clinical Science, Clinical Neuropharmacology Section, cooperated with CNRS UMR 146, Orsay, France, the University of Würzburg, Germany, and the Soroka Medical Center, Israel, on the study and treatment of obsessive-compulsive disorder, and with Libera Università, Rome, Italy, on animal models for the study of serotonin-related functional neuroanatomic and neuropharmacological changes in mutant mice.

- The Laboratory of Genetics collaborated with the University of Bonn, Germany, on the genetics of pain; with the Riken Institute, Saitama, Japan, on functional genetics; and with Hôpital Ar-razi, Salé, Morocco, on the genetics of schizophrenia.

- The Laboratory of Molecular Biology, Section on Neurobiology, worked with the University of Naples, Italy, and with Vrije

University, the Netherlands, on the compartmentalization of gene expression in the nervous system. The Section on Biophysical Chemistry collaborated with Novartis, Basel, Switzerland, in studies to develop anti-T-cell immunotoxins for the induction of transplantation tolerance and the treatment of autoimmune disease.

■ The Laboratory of Neuropsychology worked with Oxford University, England, on neural mechanisms of stimulus memory and habit formation, and with cognitive and MRI neuroscientists at the Institute of Child Health, University College, London Medical School, England, on studies of “develop-

mental amnesia” in patients who had sustained relatively selective hippocampal damage as a result of hypoxic-ischemic episodes that occurred either neonatally or later in childhood.

■ The Laboratory of Socio-Environmental Studies collaborated with Centre Régional de Médecine Traditionnelle, Bandiagara, Mali, on research on migration for work and on mental health and AIDS in Mali.

■ The Laboratory of Systems Neuroscience cooperated with Hebrew University, Jerusalem, Israel, on the neural mechanisms of motor learning and memory.

■ The Section on Pharmacology worked

with the University of Bern, Switzerland, on the role of neuropeptides and biogenic amines in neuroendocrine regulation of brain angiotensin receptor subtypes; with the Center for Endocrinological Research, National Research Council, Buenos Aires, Argentina, on the role of the angiotensin system in the regulation of stress; with the Institute of Biology and Experimental Medicine, National Research Council, Buenos Aires, on the role of angiotensin receptors in the regulation of hormone release; and with Laval University, Quebec, on the interaction of the angiotensin system and neurosteroid receptors in the brain.